Charles M. Lizza
William C. Baton
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102
(973) 286-6700
clizza@saul.com
wbaton@saul.com

Attorneys for Plaintiffs Sucampo AG, Sucampo Pharmaceuticals, Inc., Sucampo Pharma, LLC, Takeda Pharmaceutical Company Limited, Takeda Pharmaceuticals USA, Inc., and Takeda Pharmaceuticals America, Inc.

Of Counsel:

Preston K. Ratliff II
Joseph M. O'Malley, Jr.
Evan D. Diamond
Yousef M. Mian
PAUL HASTINGS LLP
200 Park Avenue
New York, NY 10166
(212) 318-6000

Attorneys for Plaintiffs Sucampo AG, Sucampo Pharmaceuticals, Inc., and Sucampo Pharma, LLC

William F. Cavanaugh
Aileen M. Fair
PATTERSON BELKNAP WEBB & TYLER LLP
1133 Avenue of the Americas
New York, NY 10036
(212) 336-2000

Attorneys for Plaintiffs Takeda Pharmaceutical Company Limited, Takeda Pharmaceuticals USA, Inc., and Takeda Pharmaceuticals America, Inc.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

SUCAMPO AG, SUCAMPO PHARMACEUTICALS, INC., SUCAMPO PHARMA, LLC, TAKEDA PHARMACEUTICAL COMPANY LIMITED, TAKEDA PHARMACEUTICALS USA, INC., and TAKEDA PHARMACEUTICALS AMERICA, INC.,

Plaintiffs,

v.

TEVA PHARMACEUTICAL INDUSTRIES LTD. and TEVA PHARMACEUTICALS USA, INC.,

Defendants.

Civil Action No. _____

COMPLAINT FOR PATENT INFRINGEMENT

(Filed Electronically)

Plaintiffs Sucampo AG, Sucampo Pharmaceuticals, Inc., and Sucampo Pharma, LLC (collectively, "Sucampo") and Takeda Pharmaceutical Company Limited, Takeda Pharmaceuticals USA, Inc., and Takeda Pharmaceuticals America, Inc. (collectively, "Takeda") (together with Sucampo, "Plaintiffs"), for their Complaint against Defendants Teva Pharmaceutical Industries Ltd. ("Teva Ltd.") and Teva Pharmaceuticals USA, Inc. ("Teva USA") (collectively, "Teva"), hereby allege as follows:

THE PARTIES

1. Sucampo AG is a Swiss corporation having a primary place of business at Baarerstrasse 22, CH-6300, Zug, Switzerland.

2. Sucampo Pharmaceuticals, Inc. is a corporation having a principal place of business at 805 King Farm Boulevard, Suite 550, Rockville, Maryland 20850.

3. Sucampo Pharma, LLC, which merged with a Japanese corporation previously known as R-Tech Ueno, Ltd., is a wholly owned subsidiary of Sucampo Pharmaceuticals, Inc., having a principal place of business at 1-1-7 Uchisaiwaicho, Chiyoda-ku, Tokyo 100-0011, Japan.

4. Takeda Pharmaceutical Company Limited is a Japanese corporation having a principal place of business at 1-1, Doshomachi 4-chome, Chuo-ku, Osaka 540-8645, Japan.

5. Takeda Pharmaceuticals USA, Inc. is a corporation jointly owned by Takeda Pharmaceutical Company Limited and non-party Takeda Pharmaceuticals International AG, having a principal place of business at One Takeda Parkway, Deerfield, Illinois 60015.

6. Takeda Pharmaceuticals America, Inc. is a wholly owned subsidiary of Takeda Pharmaceuticals USA, Inc., having a principal place of business at One Takeda Parkway, Deerfield, Illinois 60015.

7. Upon information and belief, Teva Ltd. is an Israeli company with its principal place of business at 5 Basel Street, P.O. Box 3190, Petah Tikva, 49131, Israel.

8. Upon information and belief, Teva USA is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454.

9. Upon information and belief, Teva USA is a wholly owned subsidiary of and agent for Teva Ltd.

10. Upon information and belief, Teva USA is registered with the State of New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey under Business ID No. 0100250184.

11. Upon information and belief, Teva USA is registered with the State of New Jersey's Department of Health as a drug manufacturer and wholesaler under Registration Nos. 5000583 and 5003436.

12. Upon information and belief, Teva USA has places of business located at 8 Gloria Lane, Fairfield, New Jersey 07004 and at 400 Chestnut Ridge Road, Woodcliff Lake, New Jersey 07677.

13. Upon information and belief, Teva USA develops, manufactures, and/or imports generic pharmaceutical versions of branded products for sale and use throughout the United States, including in this Judicial District. Upon information and belief, Teva USA

markets, distributes, and/or sells generic pharmaceutical versions of branded products throughout the United States, including in this Judicial District.

14. Upon information and belief, Teva Ltd., either directly or through one or more of its wholly owned subsidiaries and/or agents, develops, manufactures, and/or imports generic pharmaceutical versions of branded products for sale and use throughout the United States, including in this Judicial District. Upon information and belief, Teva Ltd., either directly or through one or more of its wholly owned subsidiaries and/or agents, markets, distributes, and/or sells generic pharmaceutical versions of branded products throughout the United States, including in this Judicial District.

JURISDICTION AND VENUE

15. This is a civil action for infringement of United States Patent Nos. 6,414,016, 8,071,613, 7,795,312, 6,982,283, 8,097,653, 8,389,542, 8,026,393, 8,338,639, and 8,748,481 (collectively, "the patents-in-suit"). This action arises under the Patent Laws of the United States, 35 U.S.C. § 100 *et seq*.

16. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

17. Venue is proper in this Court under 28 U.S.C. §§ 1391(b), (c), and/or (d), and 1400(b).

18. This Court has personal jurisdiction over, and venue is proper as to, Teva Ltd. and Teva USA because, *inter alia*, Teva Ltd. and Teva USA have each committed, or aided, abetted, contributed to, or participated in the commission of, acts of patent infringement, including acts in the State of New Jersey, that have led to foreseeable harm and injury to Plaintiffs in the State of New Jersey.

19. Upon information and belief, Teva Ltd. and Teva USA are agents of each other with respect to formulating, manufacturing, packaging, marketing, and/or selling pharmaceutical products throughout the United States, and will do the same with respect to Teva's proposed products that are the subject of Abbreviated New Drug Application ("ANDA") No. 209920, for which they have sought approval from the United States Food and Drug Administration ("FDA").

20. Upon information and belief, Teva Ltd. and Teva USA are acting in concert with each other with respect to formulating, manufacturing, packaging, marketing, and/or selling pharmaceutical products throughout the United States and will do the same with respect to Teva's proposed products that is the subject of ANDA No. 209920, for which Teva USA has sought approval from the FDA.

21. Upon information and belief, Teva Ltd, alone and/or together with its affiliate and agent Teva USA, filed or caused to be filed ANDA No. 209920 with the FDA.

22. Upon information and belief, Teva USA acts at the direction, and for the benefit, of Teva Ltd., and is controlled and/or dominated by Teva Ltd.

23. Teva USA sent Sucampo a Notice Letter dated August 14, 2017 (the "Teva Notice Letter"), stating that the FDA has received ANDA No. 209920 seeking approval to commercially manufacture, use, market, or sell generic lubiprostone capsules 8 mcg and 24 mcg (the "ANDA Products") in the United States, including, upon information and belief, in the State of New Jersey, prior to the expiration of the patents-in-suit.

24. Upon information and belief, the actions of Teva USA of, *inter alia*, filing ANDA No. 209920, sending the Teva Notice Letter to Sucampo, and maintaining its distribution channels, including in the State of New Jersey, establish that if granted approval, Teva USA will

commercially manufacture, use, offer to sell, sell, and/or import the ANDA Products throughout the United States, including in New Jersey.

25. This Court has personal jurisdiction over, and venue is proper as to, Teva USA because, *inter alia*, it: (1) has purposely availed itself of the privilege of doing business in New Jersey, including securing a New Jersey wholesale drug distributor's license (Registration Nos. 5003436 and 5000583) and a New Jersey Business Entity identification number (Registration No. 0100250184); (2) develops, manufactures, and/or imports generic pharmaceutical versions of branded products for sale and use throughout the United States, including in the State of New Jersey; (3) directly or indirectly markets, distributes, and/or sells its generic pharmaceutical drugs in the State of New Jersey; (4) directly or indirectly maintains pervasive, continuous, and systematic contacts with the State of New Jersey, including through a network of wholesalers and distributors, for the purposes of marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey; (5) has employees and places of business located at 8 Gloria Lane, Fairfield, New Jersey 07004 and 400 Chestnut Ridge Road, Woodcliff Lake, New Jersey 07677; and (6) enjoys substantial income from sales of its generic pharmaceutical drugs in the State of New Jersey.

26. Upon information and belief, Teva USA purposefully has conducted and continues to conduct business in this Judicial District. Upon information and belief, Teva USA works in concert with its agents with respect to the regulatory approval, manufacturing, marketing, sale, and distribution of its generic pharmaceutical products throughout the United States, including in this Judicial District.

27. In the Teva Notice Letter, which included an Offer of Confidential Access, Teva USA represented that it would "irrevocably submit to and accept, generally and

unconditionally the exclusive personal jurisdiction of the courts of the State of New Jersey, and of the U.S. District Court for the State of New Jersey, [and] waive[] its right to assert any objection or defense based on venue or forum *non conveniens*."

28. Teva USA did not contest venue in at least nine actions brought in this Judicial District in the last five years. *See, e.g.*, Civil Action Nos. 15-5982, 15-8663, 15-7889, 15-5909, 14-6398, 14-5878, 14-7811, 14-6341, and 14-5498.

29. Additionally, the business of Teva USA involves challenging patents held by branded pharmaceutical companies, including in this Judicial District. Teva USA has routinely consented to jurisdiction and venue in this Court, and availed itself of the protections afforded by this Court, including by asserting Counterclaims in this Court. *See, e.g., Celgene Corp. v. Par Pharmaceutical, Inc., et al.*, Civil Action No. 17-3159 (ES)(JAD) (D.N.J.); *AstraZeneca Pharmaceuticals LP, et al. v. Teva Pharmaceuticals USA, Inc., et al.*, Civil Action No. 15-7889 (RMB)(KMW) (D.N.J.); *BTG International Limited et al. v. Actavis Laboratories FL, Inc., et al.*, Civil Action No. 15-5909 (KM)(JBC) (D.N.J.). Teva USA has further availed itself of the jurisdiction of this Court by previously initiating litigation in this Court. *See, e.g.*, *Teva Pharmaceuticals USA, Inc., et al. v. Sandoz Inc., et al.*, Civil Action No. 17-0275 (FLW)(DEA) (D.N.J.); *Teva Pharmaceuticals USA, Inc., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 17-0517 (FLW)(DEA) (D.N.J.); *Teva Pharmaceuticals USA, Inc. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 15-0471 (CCC)(MF) (D.N.J.).

30. Pursuant to 28 U.S.C. § 1391(c)(3), Teva Ltd. may be sued in any judicial district because it does not reside in the United States.

31. This Court has personal jurisdiction over, and venue is proper as to, Teva Ltd. because, *inter alia*, it: (1) holds Drug Master File No. 023402 for lubiprostone, the active

pharmaceutical ingredient in the ANDA Products; (2) directs and/or controls Teva USA; (3) makes its generic pharmaceutical drugs available in the United States, including in New Jersey, through Teva USA, which has at least two places of business in New Jersey; (4) directly or indirectly markets, distributes, and/or sells its generic pharmaceutical drugs in the State of New Jersey; (5) directly or indirectly maintains pervasive, continuous, and systematic contacts with the State of New Jersey, including through a network of wholesalers and distributors, for the purposes of marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey; and (6) enjoys substantial income from sales of its generic pharmaceutical drugs in the State of New Jersey.

32. Upon information and belief, Teva Ltd. purposefully has conducted and continues to conduct business in this Judicial District. Upon information and belief, Teva Ltd. works in concert with its agents with respect to the regulatory approval, manufacturing, marketing, sale, and distribution of its generic pharmaceutical products throughout the United States, including in this Judicial District.

33. Additionally, the business of Teva Ltd. involves challenging patents held by branded pharmaceutical companies, including in this Judicial District. Teva Ltd. has routinely availed itself of the protections afforded by this Court. *See, e.g.*, *Teva Pharmaceuticals USA, Inc., et al. v. Doctor Reddy's Laboratories, Ltd., et al.*, Civil Action No. 14-5672 (MAS)(TJB) (D.N.J. Sept. 11, 2014); *Teva Pharmaceutical Industries, Ltd., et al. v. Glenmark Generics, Inc. USA, et al.*, Civil Action No. 08-4355 (GEB)(DEA) (D.N.J. Aug. 29, 2008).

34. Alternatively, to the extent the above facts do not establish personal jurisdiction over Teva Ltd., this Court may exercise jurisdiction over Teva Ltd. pursuant to Federal Rule of Civil Procedure 4(k)(2) because: (1) Plaintiffs' claims arise under federal law;

(2) Teva Ltd. would be a foreign defendant not subject to personal jurisdiction in the courts of any state; and (3) Teva Ltd. has sufficient contacts with the United States as a whole, including, but not limited to, manufacturing and selling generic pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Teva Ltd. satisfies due process.

THE PATENTS-IN-SUIT

35. Sucampo Pharmaceuticals, Inc. holds approved New Drug Application ("NDA") No. 021908, under which the FDA granted approval on January 31, 2006 for 24 mcg lubiprostone capsules and on April 29, 2008 for 8 mcg lubiprostone capsules, both marketed in the United States under the trade name AMITIZA®.

36. AMITIZA® (lubiprostone) capsules approved in NDA No. 021908 are indicated for the treatment of chronic idiopathic constipation in adults and the treatment of opioid-induced constipation in adult patients with chronic, non-cancer pain. In addition, AMITIZA® (lubiprostone) capsules are indicated for the treatment of irritable bowel syndrome with constipation ("IBS-C") in women ≥ 18 years old.

37. Sucampo AG owns United States Patent No. 6,414,016 ("the '016 patent") titled "Anti-Constipation Composition." The '016 patent was duly and legally issued on July 2, 2002. A copy of the '016 patent is attached as Exhibit A.

38. Sucampo AG owns United States Patent No. 8,071,613 ("the '613 patent") titled "Anti-Constipation Composition." The '613 patent was duly and legally issued on December 6, 2011. A copy of the '613 patent is attached as Exhibit B.

39. Sucampo AG owns United States Patent No. 7,795,312 ("the '312 patent") titled "Method for Treating Abdominal Discomfort." The '312 patent was duly and legally issued on September 14, 2010. A copy of the '312 patent is attached as Exhibit C.

40. Sucampo AG owns United States Patent No. 6,982,283 ("the '283 patent") titled "Method For Treating Drug-Induced Constipation." The '283 patent was duly and legally issued on January 3, 2006. A copy of the '283 patent is attached as Exhibit D.

41. Sucampo AG owns United States Patent No. 8,097,653 ("the '653 patent") titled "Dosage Unit Comprising a Prostaglandin Analog for Treating Constipation." The '653 patent was duly and legally issued on January 17, 2012. A copy of the '653 patent is attached as Exhibit E.

42. Sucampo AG owns United States Patent No. 8,389,542 ("the '542 patent") titled "Dosage Unit Comprising a Prostaglandin Analog for Treating Constipation." The '542 patent was duly and legally issued on March 5, 2013. A copy of the '542 patent is attached as Exhibit F.

43. Sucampo AG and Sucampo Pharma, LLC co-own United States Patent No. 8,026,393 ("the '393 patent") titled "Soft-Gelatin Capsule Formulation." The '393 patent was duly and legally issued on September 27, 2011. A copy of the '393 patent is attached as Exhibit G.

44. Sucampo AG and Sucampo Pharma, LLC co-own United States Patent No. 8,338,639 ("the '639 patent") titled "Soft-Gelatin Capsule Formulation." The '639 patent was duly and legally issued on December 25, 2012. A copy of the '639 patent is attached as Exhibit H.

45. Sucampo AG owns United States Patent No. 8,748,481 ("the '481 patent") titled "Method for Treating Gastrointestinal Disorder." The '481 patent was duly and legally issued on June 10, 2014. A copy of the '481 patent is attached as Exhibit I.

46. Takeda Pharmaceutical Company Limited is an exclusive licensee to the patents-in-suit. Takeda Pharmaceuticals USA, Inc. is a sublicensee of Takeda Pharmaceutical Company Limited. Takeda Pharmaceuticals America, Inc. is a sublicensee of Takeda Pharmaceuticals USA, Inc.

47. The patents-in-suit are listed in the FDA publication entitled, *Approved Drug Products with Therapeutic Equivalence Evaluations*, ("the Orange Book") for AMITIZA®.

TEVA'S ANDA NO. 209920 AND NOTICE LETTER

48. Upon information and belief, Teva USA and Teva Ltd. submitted or caused to be submitted ANDA No. 209920 to the FDA, including a certification with respect to the patents-in-suit under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) ("Paragraph IV Certification"), seeking approval to engage in the commercial manufacture, use, sale, or offer for sale within the United States, or importation into the United States, of the ANDA Products prior to expiration of the patents-in-suit.

49. Upon information and belief, on or about August 14, 2017, Teva USA sent the Teva Notice Letter to Sucampo. The Teva Notice Letter represented that ANDA No. 209920 contained Paragraph IV Certifications with respect to the '016, '613, '312, '283, '393, '639, '653, '542, and '481 patents, and that Teva USA sought approval of ANDA No. 209920 prior to the expiration of those patents.

50. Plaintiffs commenced this action within 45 days of the date of receipt of the Teva Notice Letter.

INFRINGEMENT OF THE PATENTS-IN-SUIT

51. Plaintiffs repeat and re-allege paragraphs 1-50 as if fully set forth herein.

52. Teva USA and Teva Ltd. are jointly and severally liable for any infringement of the patents-in-suit because, upon information and belief, Teva USA and Teva Ltd. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of ANDA No. 209920 and the Paragraph IV Certification to the FDA.

53. By seeking approval of ANDA No. 209920 to engage in the commercial manufacture, use, sale, or offer for sale within the United States, or importation into the United States, of the ANDA Products prior to the expiration of the '016, '613, '312, '283, '653, '542, '393, '639, and '481 patents, Teva has infringed one or more claims of those patents under 35 U.S.C. § 271(e)(2)(A).

54. If Teva manufactures, uses, offers to sell, or sells within the United States, or imports into the United States, the ANDA Products prior to the expiration of the '016, '613, '312, '283, '653, '542, '393, '639, and '481 patents, Teva will infringe one or more claims of those patents under 35 U.S.C. § 271(a), (b), or (c).

55. Separate and apart from assertions of invalidity, the Teva Notice Letter does not deny or dispute infringement of Claims 1-13 of the '016 patent, Claims 1-26 of the '613 patent, Claims 7-12 and 18-22 of the '312 patent, Claims 1-12 of the '283 patent, Claims 1-7 of the '653 patent, Claims 1-13 of the '542 patent, Claims 1-9 and 11-22 of the '393 patent, Claims 1-8, 10-21, and 23 of the '639 patent, and Claims 1-17 of the '481 patent.

56. Plaintiffs are entitled to relief provided by 35 U.S.C. § 271(e)(4), including an Order of this Court that the effective date of the approval of Teva's ANDA be a

date that is not earlier than the expiration date of the '016, '613, '312, '283, '653, '542, '393, '639, and '481 patents, or any later expiration of any patent term extension or exclusivity for these patents to which Plaintiffs are or become entitled.

57. Plaintiffs are entitled to a declaration that, if Teva commercially manufactures, uses, offers for sale, or sells the ANDA Products within the United States, imports the ANDA Products into the United States, or induces or contributes to such conduct, Teva will infringe the '016, '613, '312, '283, '653, '542, '393, '639, and '481 patents under 35 U.S.C. § 271(a), (b), or (c).

58. Plaintiffs will be irreparably harmed by Teva's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

PRAYER FOR RELIEF

Plaintiffs request that the Court grant the following relief:

A. An Order adjudging and decreeing that Teva has infringed the '016, '613, '312, '283, '653, '542, '393, '639, and '481 patents by submitting ANDA No. 209920 to the FDA;

B. A permanent injunction pursuant to 35 U.S.C. § 271(e)(4)(B) or 35 U.S.C. § 283 restraining and enjoining Teva, its directors, officers, agents, attorneys, affiliates, divisions, successors and employees, and those acting in concert with Teva, from infringing the '016, '613, '312, '283, '653, '542, '393, '639, and '481 patents by the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any drug product claimed in the aforementioned patents;

C. An Order pursuant to 35 U.S.C, § 271(e)(4)(A) decreeing that the effective date of any approval of ANDA No. 209920 be a date that is not earlier than the expiration date of

the ’016, ’613, ’312, ’283, ’653, ’542, ’393, ’639, and ’481 patents, or any later expiration of any patent term extension or exclusivity for the aforementioned patents to which Plaintiffs are or become entitled;

D. That Plaintiffs be awarded monetary relief to the extent Teva commercially manufactures, uses, offers for sale, or sells within the United States, or imports into the United States any product that infringes or induces or contributes to the infringement of the ’016, ’613, ’312, ’283, ’653, ’542, ’393, ’639, and ’481 patents within the United States prior to the expiration of the aforementioned patents, including any later expiration of any patent term extension or exclusivity for the patents to which Plaintiffs are or become entitled, and that any such monetary relief be awarded to Plaintiffs with prejudgment interest; and

E. Such other and further relief as the Court may deem just and proper.

Dated: September 25, 2017

By: s/ Charles M. Lizza
Charles M. Lizza
William C. Baton
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102
(973) 286-6700
clizza@saul.com
wbaton@saul.com

Attorneys for Plaintiffs Sucampo AG, Sucampo Pharmaceuticals, Inc., Sucampo Pharma, LLC, Takeda Pharmaceutical Company Limited, Takeda Pharmaceuticals USA, Inc., and Takeda Pharmaceuticals America, Inc.

Of Counsel:

Preston K. Ratliff II
Joseph M. O'Malley, Jr.
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PAUL HASTINGS LLP
200 Park Avenue
New York, NY 10166
(212) 318-6000

Attorneys for Plaintiffs Sucampo AG, Sucampo Pharmaceuticals, Inc., and Sucampo Pharma, LLC

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1133 Avenue of the Americas
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(212) 336-2000

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

Pursuant to Local Civil Rules 11.2 & 40.1, I hereby certify that the matter captioned *Sucampo AG, et al. v. Amneal Pharmaceuticals LLC*, Civil Action No. 17-2577 (PGS)(LHG) is related to the matter in controversy because it involves the same Plaintiffs and some of the same patents.

I further certify that, to the best of my knowledge, the mater in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: September 25, 2017

By: s/ Charles M. Lizza
Charles M. Lizza
William C. Baton
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102
(973) 286-6700
clizza@saul.com
wbaton@saul.com

Attorneys for Plaintiffs Sucampo AG, Sucampo Pharmaceuticals, Inc., Sucampo Pharma, LLC, Takeda Pharmaceutical Company Limited, Takeda Pharmaceuticals USA, Inc., and Takeda Pharmaceuticals America, Inc.

Of Counsel:

Preston K. Ratliff II
Joseph M. O'Malley, Jr.
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PAUL HASTINGS LLP
200 Park Avenue
New York, NY 10166
(212) 318-6000

Attorneys for Plaintiffs Sucampo AG, Sucampo Pharmaceuticals, Inc., and Sucampo Pharma, LLC

William F. Cavanaugh
Aileen M. Fair
PATTERSON BELKNAP WEBB & TYLER LLP
1133 Avenue of the Americas
New York, NY 10036
(212) 336-2000

Attorneys for Plaintiffs Takeda Pharmaceutical Company Limited, Takeda Pharmaceuticals USA, Inc., and Takeda Pharmaceuticals America, Inc.

Exhibit A

US006414016B1

(12) **United States Patent**
Ueno

(10) **Patent No.: US 6,414,016 B1**
(45) **Date of Patent: Jul. 2, 2002**

(54) **ANTI-CONSTIPATION COMPOSITION**

(75) Inventor: **Ryuji Ueno**, Potomac, MD (US)

(73) Assignee: **Sucampo, A.G.**, Zurich (GH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/655,760**

(22) Filed: **Sep. 5, 2000**

(51) **Int. Cl.**[7] **A61K 31/35**
(52) **U.S. Cl.** **514/456**
(58) **Field of Search** 514/456

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,317,032 A 5/1994 Ueno et al.

FOREIGN PATENT DOCUMENTS

EP 0 310 305 A 4/1989
WO WO 01/25099 A 4/2001

OTHER PUBLICATIONS

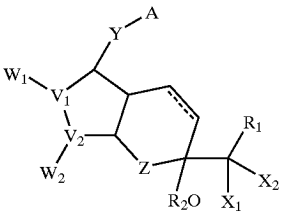
Hawley, G, Condensed Chemical Dictionary, 10th edition, 1981, p. 996.*

* cited by examiner

Primary Examiner—Rebecca Cook
(74) *Attorney, Agent, or Firm*—Sughrue Mion, PLLC

(57) **ABSTRACT**

An object of the present invention is to provide an anti-constipation composition containing a halogenated-bi-cyclic compound as an active ingredient in a ratio of bi-cyclic/mono-cyclic structure of at least 1:1. The halogenated-bi-cyclic compound is represented by Formula (I):



where X_1 and X_2 are preferably both fluorine atoms. The composition can be used to treat constipation without substantive side-effects, such as stomachache.

13 Claims, No Drawings

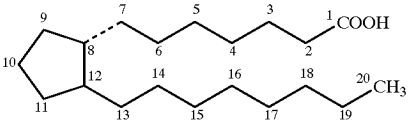
ANTI-CONSTIPATION COMPOSITION

TECHNICAL FIELD

The present invention relates to a novel therapeutic composition that contains halogenated bi-cyclic structures for treatment of constipation and use thereof.

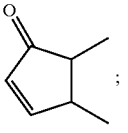
BACKGROUND OF THE INVENTION

Prostaglandins (hereinafter referred to as PGs) is the name of the group of fatty acids which possess various physiological activities and contained in human and animal tissues and organs. PGs basically contain the prostanoic acid skeleton of the following formula:



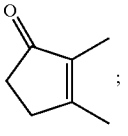
and some synthetic products may contain the above skeleton with some modification. PGs are classified into several types according to the structure and substituents on the five-membered ring, for example,

Prostaglandins of the A series (PGAs)



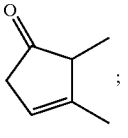
;

Prostaglandins of the B series (PGBs)



;

Prostaglandins of the C series (PGCs)



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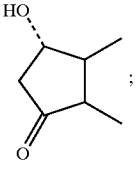
Prostaglandins of the D series (PGDs)



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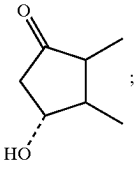
Prostaglandins of the E series (PGEs)



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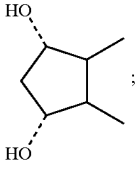
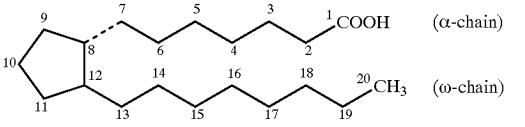
Prostaglandins of the F series (PGFs)



;

and the like. Further, they are classified into PG_1s containing a 13,14-double bond; PG_2s containing, 5,6- and 13,14-double bonds; and PG_3s containing 5,6-, 13, 14- and 17,18-double bonds.

PGs are expressed as follows. In PGs, the carbons constituting an α-chain, an ω-chain and a five-membered ring are numbered according to the basic skeleton as follows:



That is, in the basic skeleton, the constituent carbon atoms are numbered in such a way that the carbon atom in the carboxyl group is C-1, and the cc-chain contains C-2–C-7, the number increasing toward the ring, the five-membered ring contains C-8–C-12, and the ω-chain contains C-13–C-20. When the carbons of α-chain are fewer, the numbers of the carbon atoms ensuing C-2 should be properly shifted, and when more than 7, the compound is named provided that carbon at the C-2 position has substituent instead of carboxyl group (at the C-1 position). When the ω-chain contains fewer carbon atoms they should be numbered correspondingly smaller than 20, and when more than 8, the carbon atoms at the 21 position and thereafter should be regarded as a substituent. As configuration, it is considered according to that of the above essential skeleton unless otherwise described.

For example, PGD, PGE and PGF mean compounds having hydroxyl group at the C-9 and/or C-11 positions. In the present invention, PGs also include those having other group instead of the hydroxyl group on the C-9 and/or C-11-positions, they being named as 9-dehydroxy-9-substituted or 11-dehydroxy-11-substituted compounds.

In addition, PGs may include the isomers, such as bi-cyclic tautomers, optical isomers; geometrical isomers, or the like.

PGs are known to have various pharmacological and physiological activities, for example, vasodilation, inducing of inflammation, platelet aggregation, stimulating uterine muscle, stimulating intestinal muscle, anti-ulcer effect and the like. PGEs or PGFs are found to possess contraction of intestines caused by intestinal stimulation is great, while enteropooling effect is poor. Accordingly, it is impossible to use PGEs or PGFs as cathartics because of side effects such as stomachache caused by the intestinal contraction.

On the other hand, PGs having a 13,14-single bond and a C-15 constituting carbonyl group, and those having a 13,14-double bond and a C-15 constituting carbonyl group are found to exist in human or animal metabolites. These 13,14-dihydro-15-keto-prostaglandins and 15-keto-prostaglandins (hereinafter referred to as 15-keto-PGs) are known to be naturally produced metabolites by enzymatic metabolism of the corresponding PGs in vivo. These 15-keto-PGs have been reported to hardly exhibit various physiological activities that PGs possess and be pharmacologically and physiologically inactive metabolites [see, Acta Physiologica Scandinavica, 66, p.509-(1966)].

U.S. Pat. No. 5,317032 to Ueno et al. describes prostaglandin cathartics, including the existence of bi-cyclic tautomers. However, the pronounced activity as anti-constipation treatment and prevention agents of the bi-cyclic tautomers has not been heretofore known.

While estimating the pharmacological activities of the analogues of 15-keto-PGs, however, the present inventors have found that the corresponding bi-cyclic compounds, i.e., the bi-cyclic tautomers, substituted by one or more halogen atoms can be employed in small doses for relieving constipation. At the C-16 position, especially, fluorine atoms, can

be employed in small doses for relieving constipation. Where desired, larger doses to cause strong cathartic effect can be employed, although the primary purpose of the present invention is to restore a normal number of bowel movements (3 to 7 per week).

SUMMARY OF THE INVENTION

An object of the present invention is to provide a composition for treatment of constipation comprising bi-cyclic-halogenated compounds without substantive side effects such as stomachache caused by intestinal contraction. Accordingly, the bi-cyclic-halogenated compounds of the present invention may be used not only for treatment of chronic or intermittent constipation, but also for treatment or prevention of constipation (as well as to effect loose bowels when desired) in the patients suffering from constipation associated with, for example, in hernia or cardiovascular system disease, in order not to strain at stool, or suffering from proctogenic diseases. Moreover, they may be used to produce normal bowel movements for washing out harmful substances from intestine in case of drug or food poisoning. Additionally, the bi-cyclic halogenated compounds may be used as a bowel cleansing agent used for preparation of the bowel prior to preventative, diagnostic or surgical procedures.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an anti-constipation composition (prevention and/or treatment of constipation) containing bi-cyclic-halogenated compounds as active ingredients.

Cathartics work by the combination of one or more of the four mechanisms shown below, thereby increasing water content of feces and promoting transfer of the content in the intestines:

(i) Water and electrolytes may be kept in intestines owing to the hydrophilicity or osmotic pressure of the drug, thereby the intraintestinal content increased in volume which indirectly results in faster transfer thereof.

(ii) The drug may work on the intestinal mucosa to reduce total amount of normal absorption of electrolytes and water and increase the amount of water, indirectly resulting in faster transfer of the intraintestinal content.

(iii) The drug may work on the intestinal mucosa to increase total amount of normal secretion of electrolytes and water and increase the amount of water, directly and/or indirectly resulting in faster transfer of the intraintestinal content.

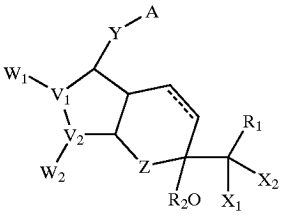
(iv) The drug firstly works on intestinal movement to fasten transfer, indirectly resulting in reduced net absorption of water and electrolytes because the time for them to be absorbed is reduced.

The enteropooling test employed in the present invention is intended to investigate mainly on the action (ii) and/or (iii), which assesses the effect of the drug on the intraintestinal water pool by measuring the volume of the intraintestinal content. The bi-cyclic-halogenated compounds of the present invention may show extremely great enteropooling effect. However, they hardly or slightly cause contraction of intestines which is one of indexes for assessment of the action (iv). Accordingly, the bi-cyclic-halogenated compounds of the present invention are considered to alleviate constipation by mainly acting on intestinal mucosa directly or indirectly to affect transfer of electrolytes and water from

intestinal walls into blood vessels and/or from blood vessels into intestines, resulting in reduced water absorption and/or in increased water secretion through the intestines, increased intraintestinal water pool and promoted transfer of the intraintestinal content.

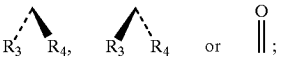
A preferred compound used in the present invention is represented by formula (I):

Formula (I)



where V_1 and V_2 are carbon or oxygen atoms;

W_1 and W_2 are



R_3 and R_4 are both hydrogen atoms or one of them is OH;

X_1 and X_2 are hydrogen, lower alkyl or halogen atom, and at least one of these is a halogen atom;

Z is a carbon, oxygen, sulfur or nitrogen atom;

R_2 is a hydrogen atom or lower alkyl;

Y is a saturated or unsaturated $C_{2\text{-}10}$ hydrocarbon chain which is unsubstituted or substituted by oxo, halogen, an alkyl group, hydroxyl or aryl;

A is $-CH_2OH$, $-COCH_2OH$, -COOH or its functional derivative; and

R_1 is a saturated or unsaturated, lower hydrocarbon forming a straight-chain, a branched-chain or a ring, which is unsubstituted or substituted by halogen, oxo, hydroxy, lower alkoxy, lower alkanoyloxy, lower cycloalkyl, lower cycloalkyloxy, aryl, or aryloxy. Preferably R_1 is not substituted. Where a substituent is present, care must be exercised to avoid possible steric hinderance in formation of the bi-cyclic compound from or in association with the corresponding monocyclic PGs.

The steric configuration of C-15 can be R, S, or a mixture thereof.

The bond between C-13 and C-14 position can be a single or double bond.

In the above formula, the term "unsaturated" is intended to include at least one or more double bonds and/or triple bonds that are isolatedly, separately, or serially present between the carbon atoms of the main and/or side chains. An unsaturated bond between two serial positions is represented by denoting the lower number of the two positions, and an unsaturated bond between two distal positions is represented by denoting both of the positions.

Preferred unsaturated bonds are a double at position 2 and a double or triple bond at position 5.

The term "lower" is intended to include a group having 1 to 8 carbon atoms, unless otherwise specified.

The term "ring" includes lower cycloalkyl, lower cycloalkoxy, aryl or aryloxy.

The term "halogen" includes fluorine, chlorine, bromine, or iodine atom. Particularly preferable is a fluorine atom.

The term "lower alkoxy" refers to a group of lower alkyl-O—, wherein lower alkyl is a straight or branched chain saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methyl, ethyl, propyl, isopropyl, buyl, isobutyl, t-butyl, pentyl and hexyl.

The term "hydroxy(lower)alkyl" refers to a lower alkyl as defined above which is substituted with at least one hydroxy group such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 1-methyl-1-hydroxyethyl.

The term "lower alkanoyloxy" refers to a group represented by the formula RCO—O—, wherein RCO—is an acyl group formed by oxidation of a lower alkyl group as defined above, such as acetyl.

The term "lower cycloalkyl" refers to a cyclic group formed by cyclization of a lower alkyl group as defined above but contains three or more carbon atoms, and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "lower cycloalkyloxy" refers to the group of lower-cycloalkyl-O—, wherein lower cycloalkyl is as defined above.

The term "aryl" may include unsubstituted or substituted aromatic carbocyclic or heterocyclic groups (preferably mono-cyclic groups), for example, phenyl, naphthyl, tolyl, xylyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, furzanyl, pyranyl, pyridyl, pyridazyl, pyrimidryl, pyrazyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidino, piperazinyl, morpholono, indolyl, benzothienyl, quinolyl, isoquinolyl, puryl, quinazolinyl, carbazolyl, acridinyl, phenathridinyl, benzimidazolyl, benzimidazolonyl, benzothiazolyl and phenothiazinyl. Examples of substituents are halogen atom and halo(lower)alkyl, wherein halogen atom and lower alkyl are as defined above.

The term "aryloxy" refers to a group represented by the formula Ar—O, wherein Ar is aryl as defined above.

The bi-cyclic-16-halogen compounds used in the present invention may be salts or those with an esterified carboxyl group or etherified group. Such salts include pharmaceutically acceptable salts, for example, those of alkali metals such as sodium, potassium; those of alkaline earth metals such as calcium, magnesium; those of physiologically acceptable ammonium salts such as ammonia, methylamine, dimethylamine, cyclopentylamine, cyclohexylamine, benzylamine, piperidine, ethylenediamine, monoethanolamine, diethanolamine, triethanolamine, monomethylmonoethanolamine, trometamine, lysine, procaine, caffeine, arginine, tetralkylammonium salt and the like. These salts may be prepared by a conventional process, for example, from the corresponding acid and base or by salt interchange.

Such esters and ethers include, for example, straight or branched alkyl esters and ethers which may contain one or more unsaturated bonds such as methyl, ethyl, propyl, butyl, isopropyl, isobutyl, t-butyl, pentyl, 2-ethylhexyl; those having an alicyclic group such as a cyclopropyl, cyclopentyl or cyclohexyl group; those containing an aromatic group such as a benzyl or phenyl group (wherein the aromatic group may contain one or more substituents); a lower alkenyl such as ethynyl and propynyl, hydroxyalkyl or alkoxyalkyl such as hydroxyethyl, hydroxyisopropyl, polyhydroxyethyl, polyhydroxyisopropyl, methoxyethyl, ethoxyethyl or methoxyisopropyl ester or ether; optionally substituted aryls such as phenyl, tosyl, t-butylphenyl, salicyl, 3,4-dimethoxyphenyl and benzamidophenyl; alkylsilyls such as a trimethylsilyl or triethylsilyl; or a tetrahydropyranyl ester or ether.

Preferred esters and ethers include, for example, straight-chain or branched lower alkyl such as methyl, ethyl, propyl, n-butyl, isopropyl or t-butyl; a benzyl; or hydroxyalkyl such as a hydroxyethyl or hydroxyisopropyl.

Preferred A is —COOH or its pharmaceutically acceptable salt or ester.

Preferred X_1 and X_2 are both being halogen atoms, and more preferably, fluorine atoms.

Preferred W_1 is =O.

Preferred W_2 is where R_3 and R_4 are both hydrogen atoms.

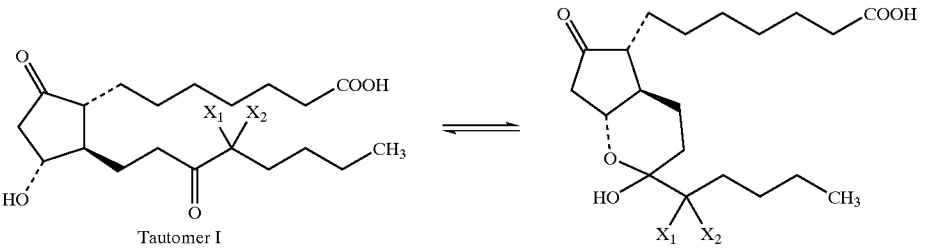
Preferred Z is an oxygen atom.

Preferred Y is an unsubstituted saturated or unsaturated hydrocarbon chain having 6–8 carbon atoms.

Preferred R_1 is an unsubstituted saturated or unsaturated hydrocarbon chain having 4–8 carbon atoms.

R_2 is preferably a hydrogen atom.

The composition of the present invention may include the isomers of the above compounds. Examples of such isomers include mono-cyclic tautomers having a keto group at the C-15 position and halogen at the C-16 position; optical isomers; geometrical isomers and the like.



The tautomerism between the oxygen atom at the C-11 position and the keto group at the C-15 position, shown above, is especially significant in the case of compounds having a 13,14-single bond and two fluorine atoms at the C-16 position.

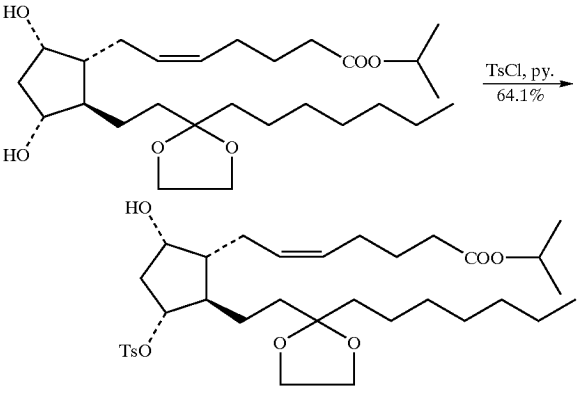
It has been discovered that in the absence of water, compounds represented by Formula (I) exist predominantly in the form of the bi-cyclic compound. In aqueous media, it is believed that hydrogen bonding occurs between, for example, the ketone position at the C-15 position, thereby hindering bi-cyclic ring formation. In addition, it is believed that the halogen atom(s) at the C-16 position promote bi-cyclic ring formation. The mono-cyclic/bi-cyclic structures, for example, may be present in a ratio of 1:6 in D_2O; 1:10 in CD_3OD-D_2O and 4:96 in $CDCl_3$. Accordingly, a preferable embodiment of the present invention is the composition in which the bi-cyclic form is present in ratio of

bi -cyclic/mono-cyclic of least 1:1, and preferably 20:1, or even greater to substantially all bi-cyclic compound; 100% bi-cyclic compound is within this invention.

The above described bi-cyclic-16-halogen compound may prepared according to the general process set forth below:

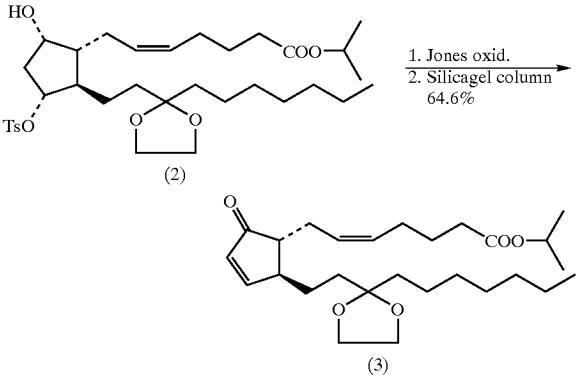
Preparation of Isopropyl 7-[(1S,3S,6S,7R)-3-Heptyl-3-hydroxy-bi-cyclo[4.3.0]nonane-8-one-7-yl] hept-5-enoate and Isopropyl 7-[1R,3S,6S,7R)-3-heptyl-3-hydroxy-bicyclo[4.3.0]nonane-8-one-7-yl] hept-5-enoate

1. Preparation of Isopropyl (Z)-7-[1R,2R,3R,5S)-2-(3,3-Ethylenedioxydecyl)-5-hydroxy-3-(p-toluensulfonyl) cyclopentyl]hept-5-enoate (2)



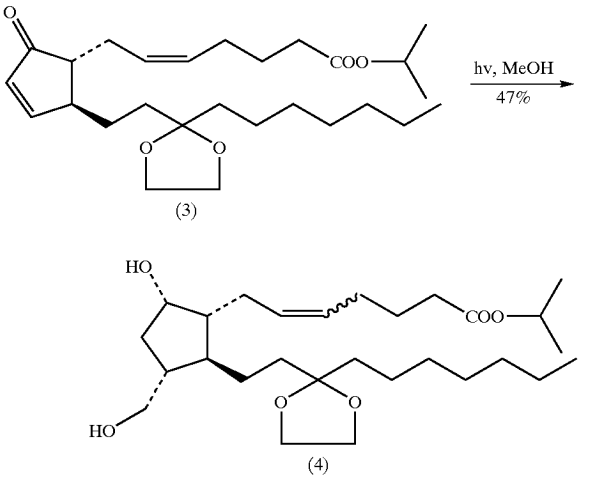
To a mixture of pyridine (0.77g) and isopropyl(Z)-7-[(1R, 2R,3R,5S)-3,5-dihydroxy-2-(3,3-ethylenedioxydecyl) cyclopentyl]hept-5-enoate (1) (4.05 g) in dichloromethane, a solution of tosyl chloride (1.86 g) in dichloromethane was added at 0° C., and stirred for 2 days at the temperature. During the reaction, each tosyl chloride (5.58 g) and pyridine (2.31 g) was added in three portions. After the usual work-up, the crude product was chromatographed on silica gel to give isopropyl (Z)-7-[(1R,2R,3R,5S)-2-(3,3-ethylenedioxydecyl)-5-hydroxy-3-(p-toluenesulfoxy) cyclopentyl]hept-5-enoate (2). Yield 3.45 g, 64.1%.

2. Preparation of Isopropyl (Z)-7-[(1R,2S)-2-(3,3-Ethylenedioxydecyl)-5-oxocyclopent-3-enyl]hept-5-enoate (3)



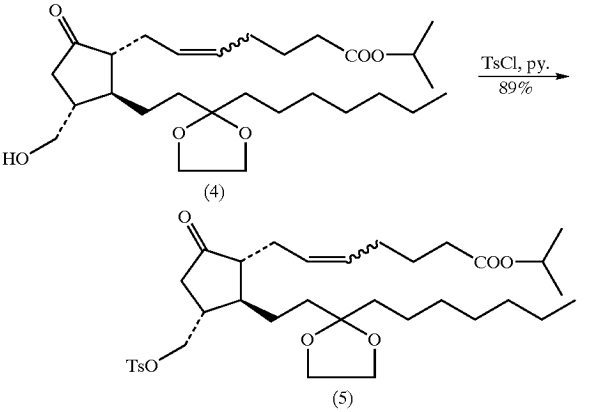
Isopropyl (Z)-[1R,2R,3R,5S)-2-(3,3-ethylenedioxydecyl)-5-hydroxy-3-(p-toluenesulfoxy) cyclopentyl]hept-5-enoate (2) (1.72 g) was oxidized in acetone at −40° C. to −20 C. with Jones reagent for 4 hours. After the usual work-up, the crude product was passed through silica gel pad with n-hexane/ethyl acetate (3.5/1). The product was further chromatographed on silica gel (n-hexane/ethyl acetate =4/1). Isopropyl (Z)-7-[(1R,2S)-2-(3,3-ethylenedioxydecyl)-5-oxo-cyclopent-3-enyl]hept-5-enoate (3) was obtained. Yield 0.81 g, 64.6%.

3. Preparation of Isopropyl-7-[(1R,2S,3R)-2-(3,3-Ethylenedioxydecyl)-3-hydroxymethyl-5-oxocyclopentyl] hept-5-enoate (4)



Isopropyl (Z)-7-[(1R,2S)-2-(3,3-ethylenedioxydecyl)-5-oxo-cyclopent-3-enyl]hept-5-enoate (3) (0.81 g) and benzophenone were dissolved in methanol. Under argon atmosphere, the solution was irradiated with 300-W high-pressure mercury lamp for 4 hours and 40 minutes. After evaporation of the solvent, the crude product was chromatographed on silica gel (n-hexane/ethyl acetate =3/2) to give isopropyl-7-[(1R,2S,3R)-2-(3,3-ethylenedioxydecyl)-3-hydroxymethyl-5-oxocyclopentyl]hept-5-enoate (4). Yield 0.41 g, 47%.

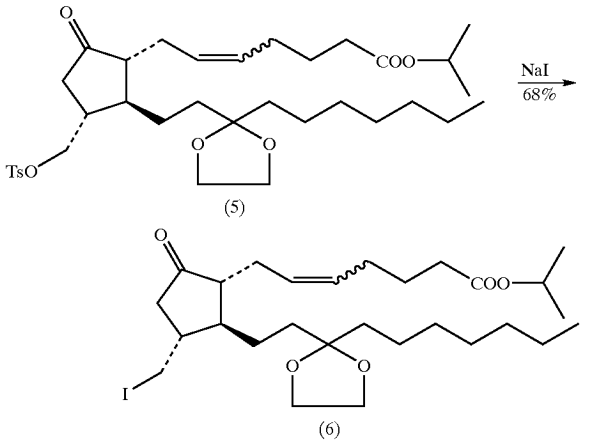
4. Preparation of Isopropyl-7-[1R,2S,3R)-2-(3,3-Ethylenedioxydecyl)-5-oxo-3-(p-toluenesuffoxymethyl) cyclopentyl]hept-5-enoate (5)



Isopropyl-(1R,2S,3R)-2-(3,3-ethylenedioxydecyl)-3-hydroxymethyl-5-oxocyclopentyl]hept-5-enoate (4) (0.21 g) and pyridine (0.07 g) were dissolved in dichloromethane. To

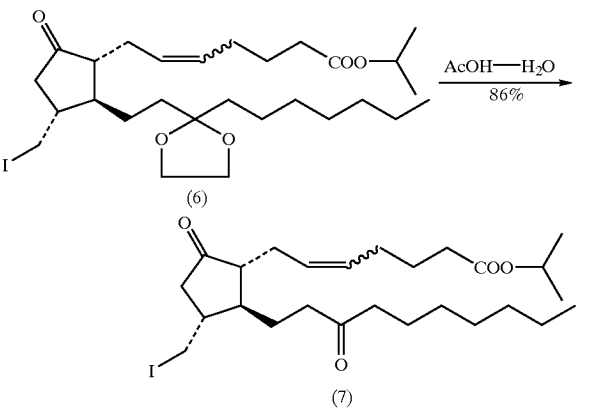
this solution, tosyl chloride (0.17 g) was added at 0° C., and the mixture was stirred for 72 hours. After the usual work-up, the crude product was chromatographed on silica gel to give isopropyl 7-(1R,2S,3R)-2-(3,3-ethylenedioxydecyl)-5-oxo-3-(p-toluenesulfoxy)methylcyclopentyl]hept-5-enoate (5). Yield 0.25 g, 89%.

5. Preparation of Isopropyl-7-[(1R,2R,3R)-2-(3,3-Ethylenedioxydecyl)-3-iodemethyl-5-oxocyclopentyl] hept-5-enoate (6)



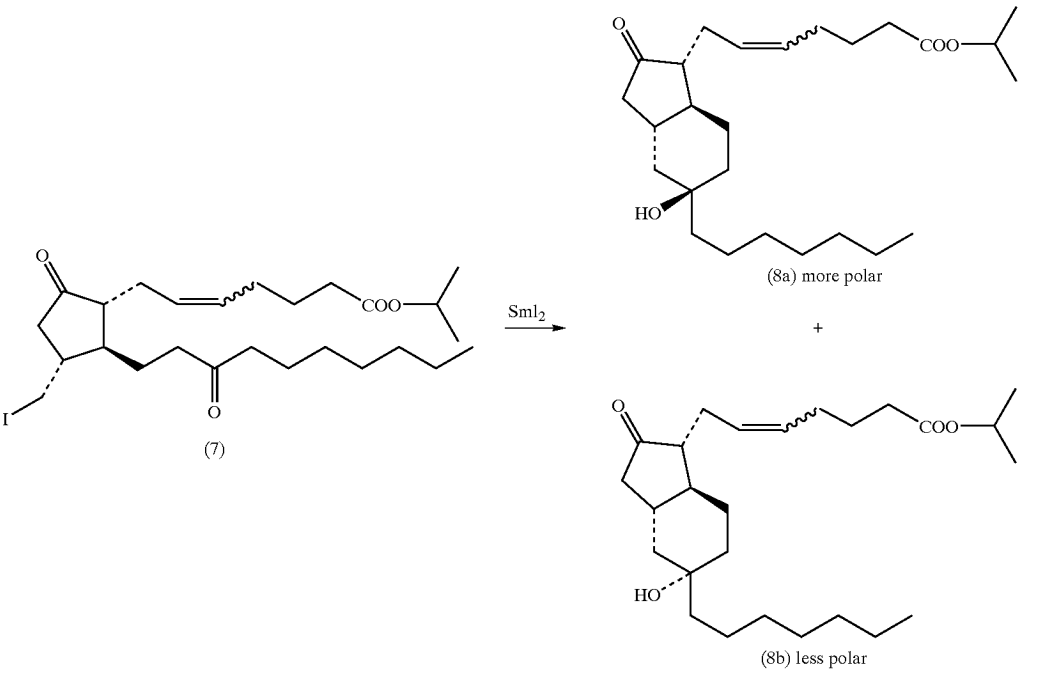
Isopropyl 7-(1R,2S,3R)-2-(3,3-ethylenedioxydecyl)-5-oxo-3-(p-toluenesulfoxy)methylcyclopentyl]hept-5-enoate (5) (0.25 g) was dissolved in acetone, and sodium iodide (0.12 g) was added. The mixture was refluxed for 3 hours. Sodium iodide (0.097 g) was added to the mixture, and the mixture was refluxed for additional 80 minutes. After the usual work-up, the crude product was chromatographed on silica gel (n-hexane/ethyl acetate =5/1) to give isopropyl 7-(1R,2R,3R)-2-(3,3-ethylenedioxydecyl)-3-iodemethyl-5-oxocyclopentyl]hept-5-enoate (6). Yield 0.16 g, 68%.

6. Preparation of Isopropyl 7-(1R,2R,3R)-3-Iodemethyl-5-oxo-2-(3-oxodecyl)cyclopentyl]hept-5-enoate (7)



Isopropyl 7-(1R,2R,3R)-2-(3,3-ethylenedioxydecyl)-3-iodemethyl-5-oxocyclopentyl]hept-5-enoate (6) (0.16 g) was dissolved in a mixed solvent of acetic acid/water/tetrahydrofuran (3/1/1). The mixture was stirred for 20 hours at room temperature and for 2.5 hours at 50° C. After evaporation of the solvent, the obtained residue was chromatographed on silica gel (n-hexane/ethyl acetate=1/1) to give isopropyl 7-(1R,2R,3R)-3-iodemethyl-5-oxo-2-(3-oxodecyl)cyclopentyl]hept-5-enoate (7). Yield. 0.13 g; 86%.

7. Preparation of Isopropyl 7-(1S,3S,6S,7R)-3-Heptyl-3-hydroxy-bicyclo[4.3]nonane-8-one-7-yl]hept-5-enoate (8a) and Isopropyl 7-(1S,3R,6S,7R)-3-heptyl-3-hydroxy-bicyclo [4.3.0]nonane-8-one-7-yl]hept-5-enoate (8b)

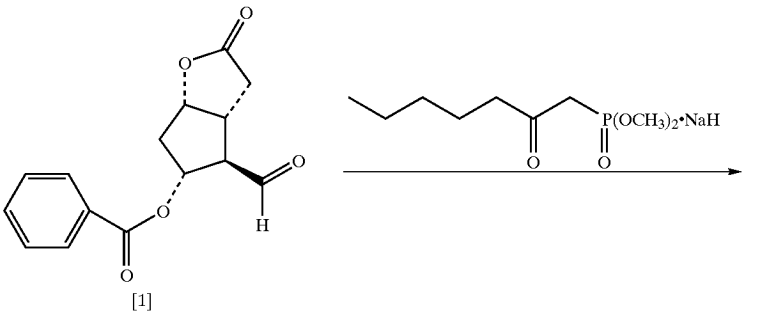


Isopropyl 7-(1R,2R,3R)-3-iodemethyl-2-(3-oxodecyl)-5-oxocyclopentyl]hept-5-enoate (7) (0.0574 g) and zirconocene dichloride were dissolved in tetrahydrofuran. The mixture was sonicated under argon stream to purge the air

out from the mixture. To the mixture samarium iodide in tetrahydrofuran (0.1 M, 2.1 mL) was added dropwise. The mixture was stirred for 30 minutes at room temperature, and then hydrochloric acid (0.1M, 1 mL) was added. After the usual work-up, the crude product was chromatographed on silica gel (n-hexane/ethyl acetate=5/1). Two bicyclic products, more polar (8a) and its epimer, less polar (8b) and starting material (7) were obtained as follows:

Isopropyl 7-(1S,3S,6S,7R)-3-heptyl-3-hydroxy-bicyclo [4.3.0]nonane-8-one-7-yl]hept-5-enoate (8a) and Isopropyl 7-(1S,3R,6S,7R)-3-heptyl-3-hydroxy-bicyclo[4.3.0] nonane-8-one-7-yl]hept-5-enoate (8b): Yield 8(a) 5.1 mg, Yield 8(b) 7.2 mg, Recovery of starting material (7) 26.7 mg.

A theoretical synthesis for a compound represented by Formula (I) where Z is a sulfur atom and W_1 is an —OH group is set forth below:



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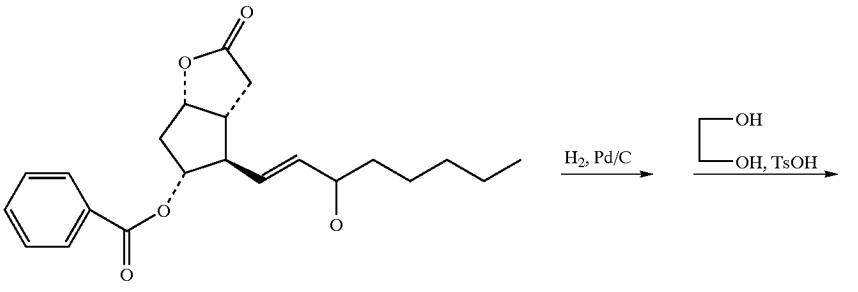
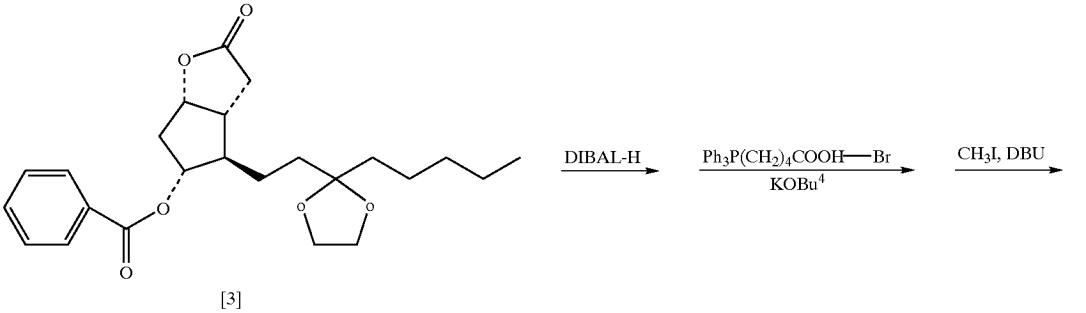
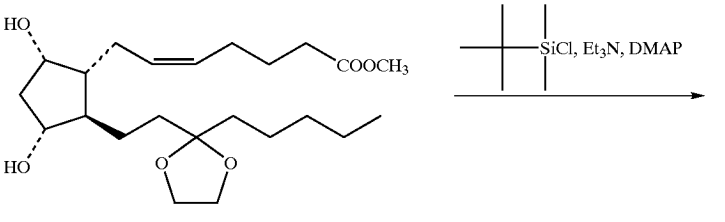


[2]



[3]



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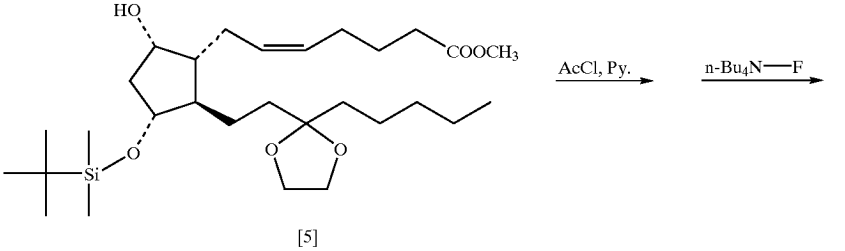
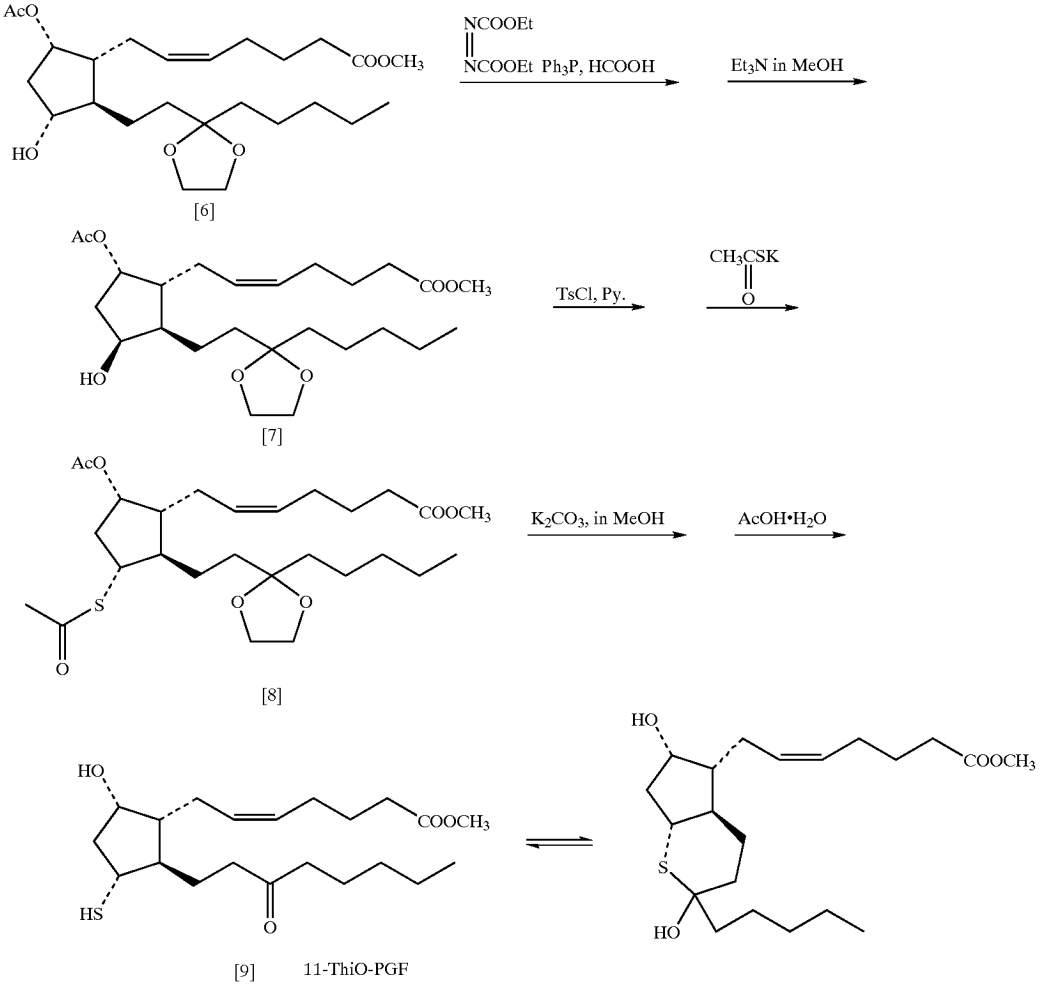


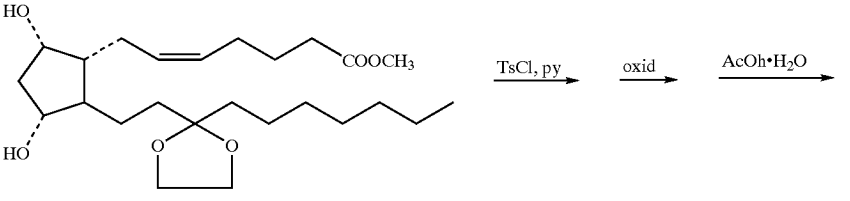
[5]

-continued



n-Bu_4N—F: tetrabutylammonium fluoride
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H: diisobutylaluminum hydride
DMAP: 4-dimethylaminopyridine
$NaBH_4$: sodium borohydride

A theoretical synthesis for a compound represented by Formula (I) where Z is a sulfur atom and W_1 is a keto is set forth below:



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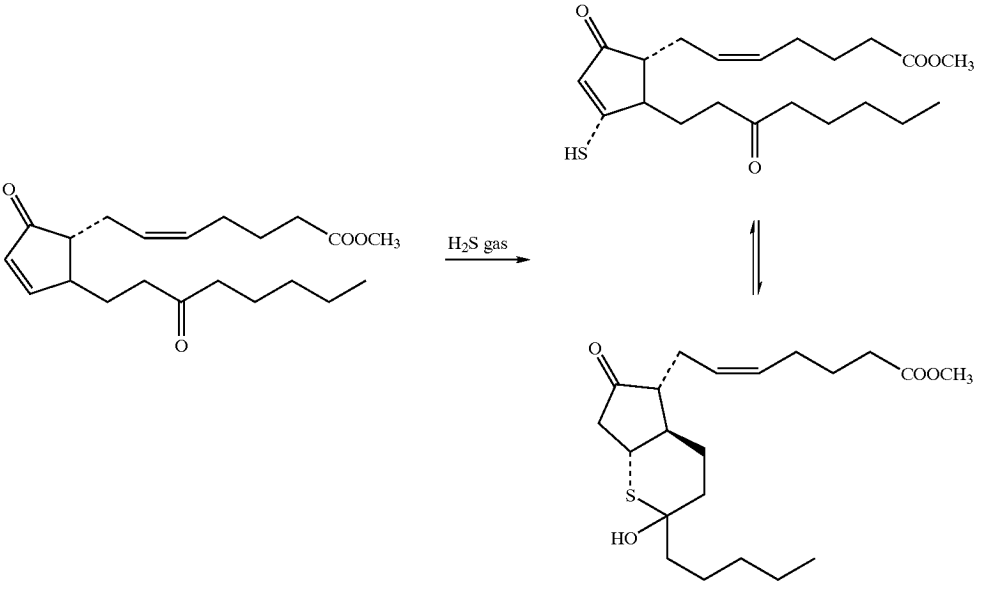
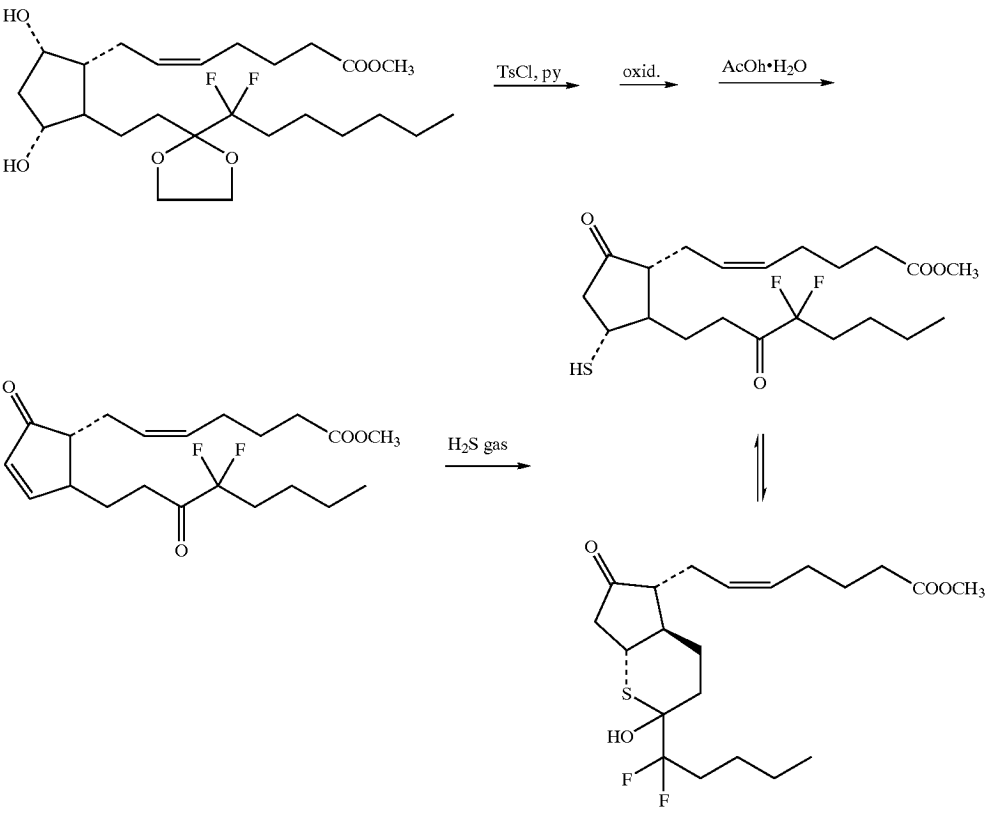
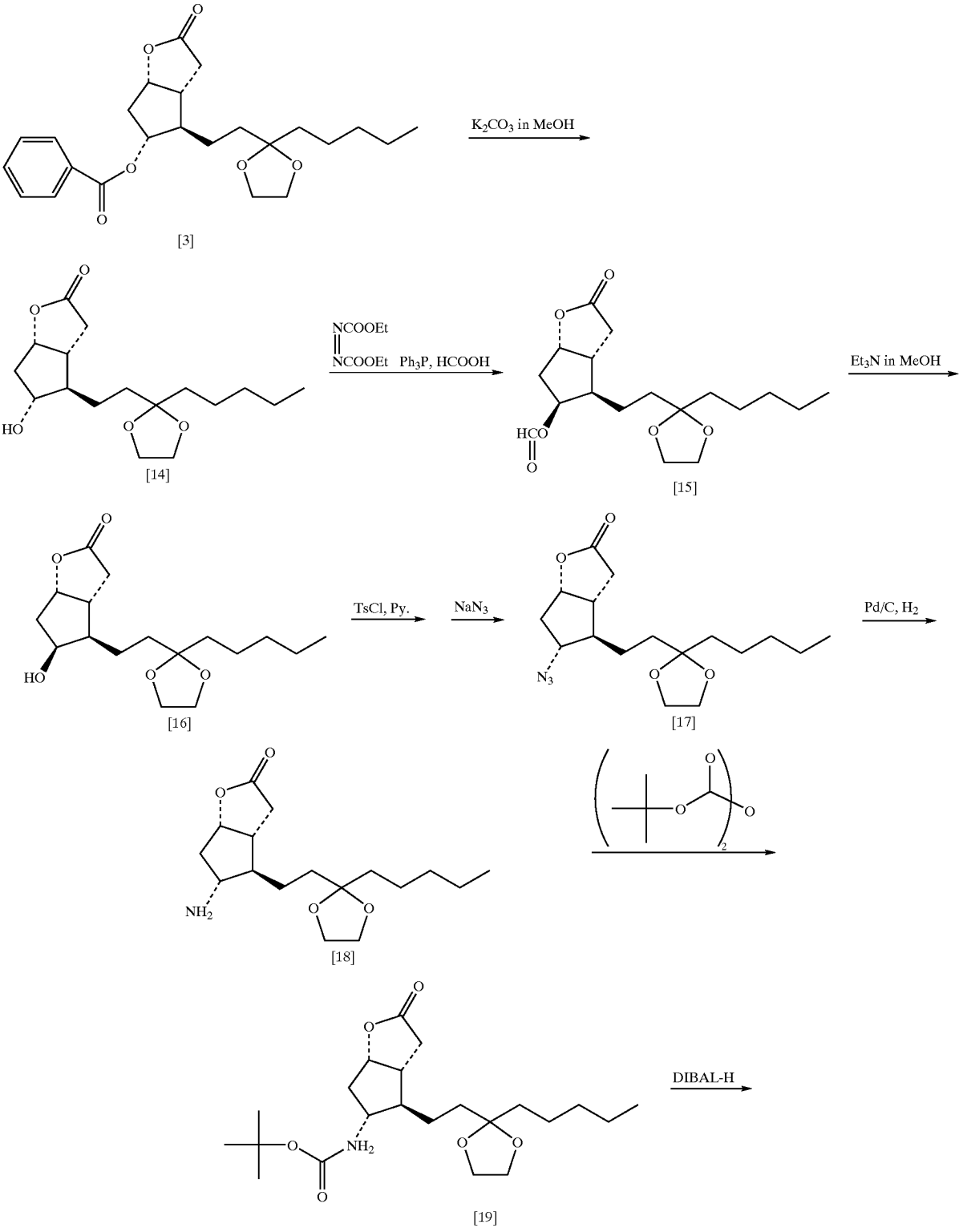


25

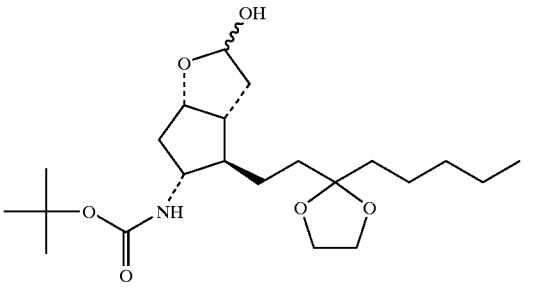
A theoretical synthesis for a compound represented by Formula (I) where Z is a sulfur atom, W_1 is a keto and X_1 and X_2 are fluorine atoms is set forth below:



A theoretical synthesis for a compound represented by Formula (I) where Z is a nitrogen atom is set forth below:


K2CO3 in MeOH
[3]
NCOOEt
NCOOEt Ph3P, HCOOH
Et3N in MeOH
HO
[14]
HCO
O
[15]
TsCl, Py.
NaN3
Pd/C, H2
HO
[16]
N3
[17]
NH2
[18]
DIBAL-H
NH2
[19]

-continued

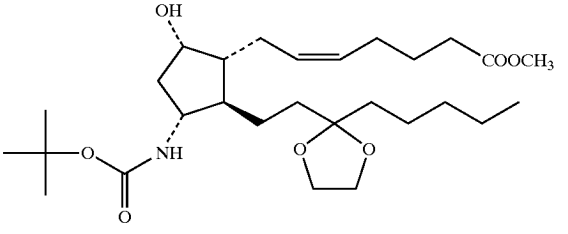


$Ph_3P(CH_2)_4COOH—Br$

$KOBu^4$

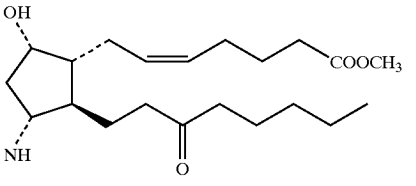
CH_3I, DBU

[20]



CF_3COOH

[21]



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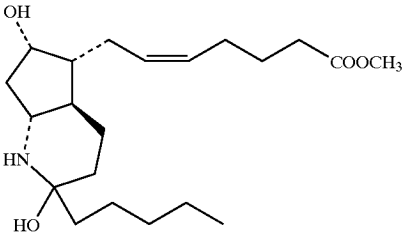
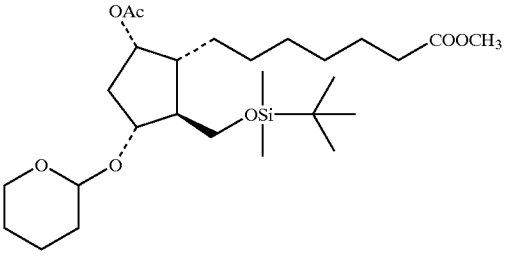


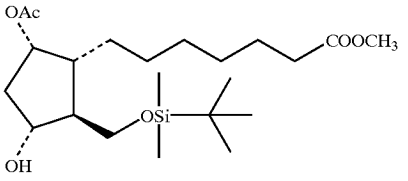
[23]

Another theoretical synthesis of a compound represented by Formula (I) where Z is a nitrogen atom is set forth below:



Et_2AlCl

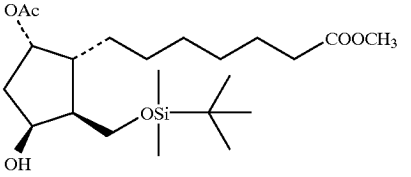
[25]



NCOOEt
||
NCOOEt Ph_3P, HCOOH

Et_3N in MeOH

[26]



TsCl, Py.

NaN_3

[27]

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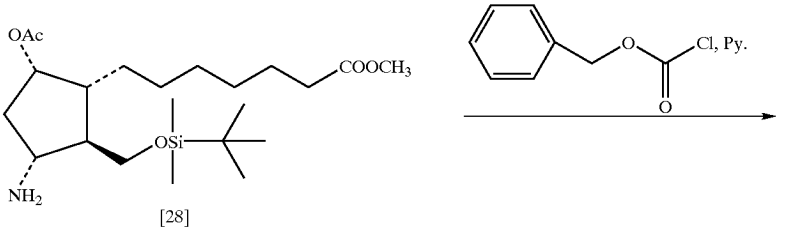

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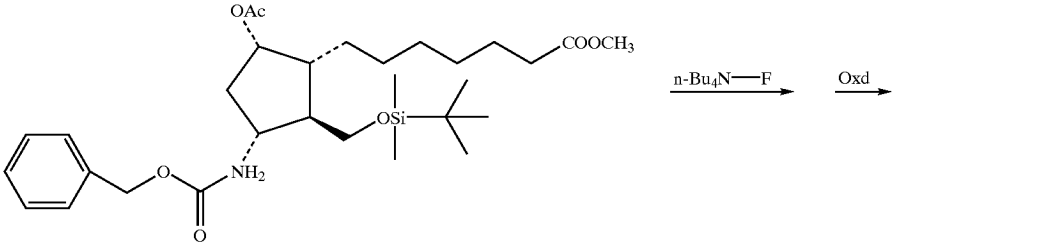

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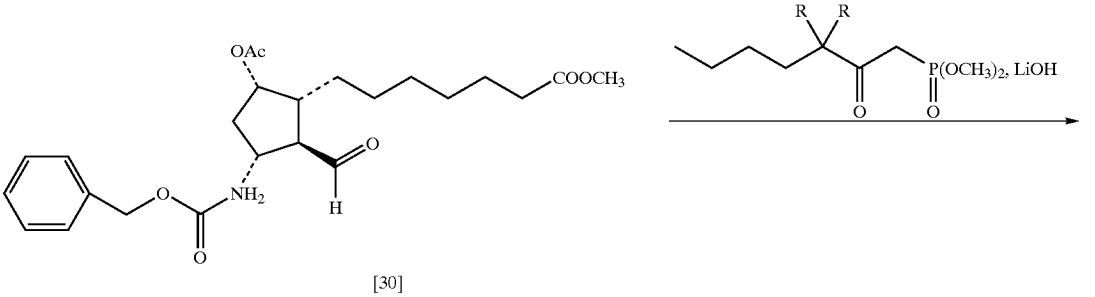

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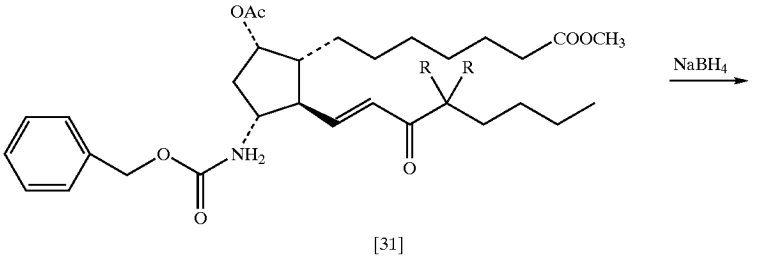
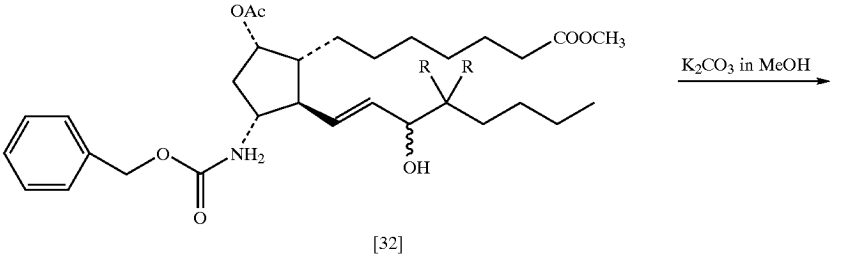
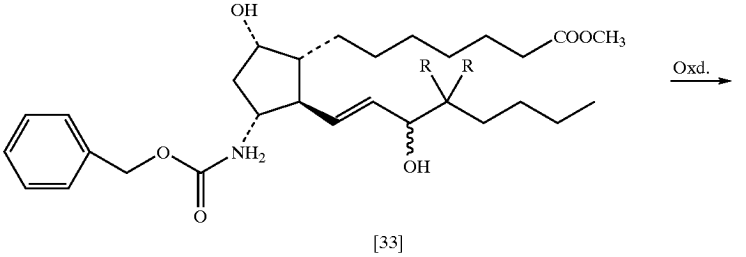


[31]

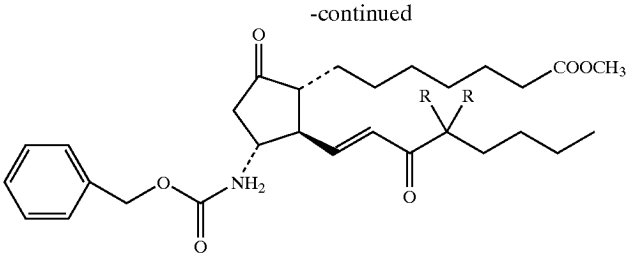


[32]

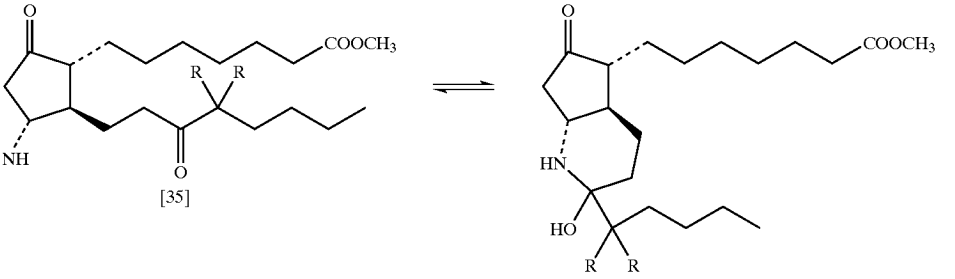


[33]

-continued



[34]



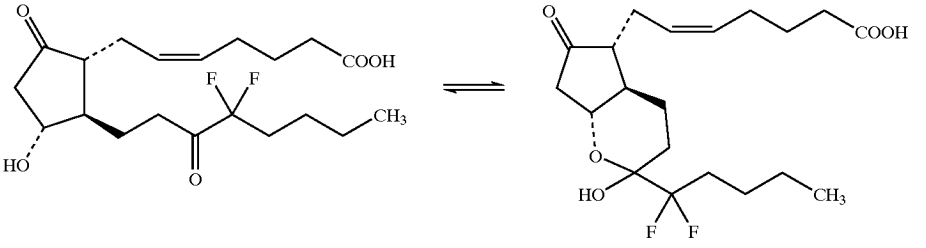
[35] [36]

R = H or F

The preparations in the present invention are not construed to be limited to them, and suitable means for protection, oxidation, reduction and the like may be employed.

In the bi-cyclic-16-halogen compounds used in the present invention, enteropooling activity is remarkably enhanced when substituted by two halogen atoms, especially fluorine atoms, at the C-16 position independently of the structure and substituents of the five-membered ring or the existence of the double bonds or other substituents. Particularly preferable bi-cyclic-16-halogen compounds are those tautomers formed from mono-cyclic compounds having a ketone at the C-9 position and a hydroxyl group at the C-11 position in the five membered ring. Another preferable group is a bi-cyclic-16-halogen compound containing a 5,6-single bond, 5,6-double bond or those having the carbon number 20–22 where R_1 contains 4 to 6 carbon atoms preferably in a straight chain.

An example of a mono-cyclic/bi-cyclic-16-halogen compound containing a 5,6-double bond are set forth below:



Another embodiment of the present invention comprises the composition of the present invention and a medium chain fatty acid triglyceride. The triglyceride may be a saturated or unsaturated fatty acid having 6–14 carbon atoms that may have a branched chain. A preferred fatty acid is a straight chain saturated fatty acid, for example, caproic acid, caprylic acid, capric acid, lauric acid and myristic acid. 2 or more medium chain fatty acid triglycerides may be used as a mixture.

The composition of the present invention may be dissolved or admixed in the medium chain fatty acid triglyceride. The amount of the medium chain fatty acid triglyceride is not limited. However, generally, 1–1,000,000 parts by weight of the medium chain fatty acid triglyceride based on one part by weight of the bi-cyclic structure may be used. Preferably, 5–500,000 parts by weight, and more preferably 10–200,000 parts by weight.

Examples of the medium chain fatty acid triglyceride used in the present 25 invention include a triglyceride of a saturated or unsaturated fatty acid having 6–14 carbon atoms which may have a branched chain. Preferred fatty acid is a straight chain saturated fatty acid for example caproic acid (C6), caprylic acid (C8), capric acid (C10), lauric acid (C12) and myristic acid (C14). In addition, 2 or more medium chain fatty acid triglycerides may be used.

Even more non-polar solvents, such as commercially available Miglyol can be employed to increase the bi-cyclic/mono-cyclic ratio.

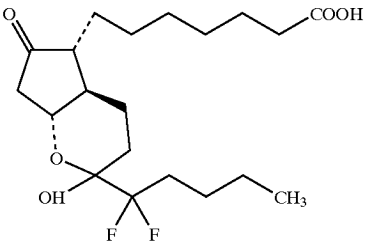
To exemplify formulation of an embodiment of the present invention and to illustrate potential effect of steric hinderance, an Example is set forth.

EXAMPLE

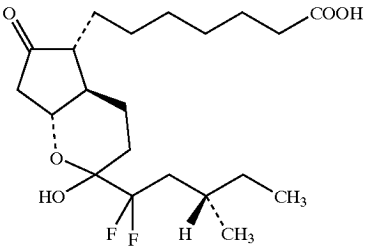
The following compounds 1 and 2 were dissolved in a medium chain fatty acid triglyceride (MCT=mixture of

caprylic acid triglyceride and capric acid triglyceride in a ratio of 85:15) in an amount shown in the table below.

compound 1



compound 2



Each of the solutions was placed in a container made of hard glass and stored at 40° C. The time-course content of compound 1 and 2 in the solutions were determined by HPLC method. At the same time, each of compounds 1 and 2 was placed solely (without being dissolved in the solvent) in the container as above, and stored at 40° C. to provide control study.

(1) In the absence of the solvent, the content of the compounds was determined as follows by the HPLC method.

Stored compounds 1 and 2, and standard compounds 1 and 2 were weighed precisely around 0.025 g each, and exactly 5 mL aliquots of internal standard solution were added to the respectively weighed compounds. Test and standard preparations were obtained by adding acetonitrile (liquid chromatograph grade) to give the precise total amount of 10 mL each. Each 10 μL of the test and standard preparations were loaded on liquid chromatograph and determined the content of the compound by internal standard method with one

$$\text{content (\%)} = \frac{Q_T}{Q_S} \times W_S \times \frac{100}{W_T}$$

W_X: The amount of the compound in the standard preparation (mg)

W_T: The amount of compound 1 and 2 in the test preparation.

Q_S: Peak area ratio of the compound in the standard preparation to the internal standard.

Q_T: Peak area ratio of the compound in the test preparation to the internal standard.

Measurement conditions:

Detector: Ultraviolet absorption spectrophotometer (wavelength 294 nm)

Column: A stainless tube having about 5 mm of internal diameter and about 25 cm of length, packed with 5 μm octadecylsilyl silica gel for liquid chromatograph

Column temperature: Stable around 35° C.

Mobile phase: Mixed solution of acetonitrile (liquid chromatograph grade)/aqueous sodium acetate (0.01 mol/L)/glacial acetic acid (800:200:1)

(2) In the presence of the solvent, the content of the compound was determined as follows by HPLC method.

Based on the value expressed in the above table, an amount of the solution corresponding to 36 μg of compounds 1 and 2 was weighed precisely. Precisely 1.0 mL of an internal standard solution was added, and then ethyl acetate (liquid chromatograph grade) was added to give a total amount of 10 mL each. Each 0.1 mL of the solution was vacuum concentrated to dryness to give the test preparation.

Each 18 mg of the standard compounds was weighed precisely and admixed with ethyl acetate (liquid chromatograph grade) to give the total amount of exactly 50 mL each. 1.0 mL of the solution and 10.0 mL of the internal standard solution were measured precisely and admixed with ethyl acetate (liquid chromatograph grade) to give a total of 100 mL each. Each 0.1 mL of the solution was vacuum concentrated to dryness to give the standard preparation.

To the test and standard preparations, 0.1 mL of fluorescent labeling reagent and 0.85 mL of fluorescent labeling catalyst were added, respectively, and the mixture was stirred and reacted at room temperature for more than 30 minutes. 0.05 mL aliquots of acetonitrile (liquid chromatograph grade) containing 2% acetic acid were added to the reaction mixtures, respectively, stirred, and then allowed to stand for more than 30 minutes to provide test and standard solutions.

Each 10 μL of the test and standard solution was loaded on liquid chromatograph and determined the content of the respective compounds by internal standard method with one point calibration curve.

$$\text{content (\%)} = \frac{Q_T}{Q_S} \times W_S \times \frac{100}{18}$$

W_X: The amount of the compound in the standard preparation (mg)

Q_S: Peak area ratio of the compound in the standard preparation to the internal standard.

Q_T: Peak area ratio of the compound in the test preparation to the internal standard.

Measurement conditions:

Detector: Fluorescent spectrometer (excitation wavelength 259 nm; fluorescent wavelength 394 nm)

Column: A stainless tube having about 5 mm of internal diameter and about 25 cm of length, packed with 5 μm octadecylsilyl silica gel for liquid chromatograph

Column temperature: Stable at around 35° C.

Mobile phase: Mixed solution of acetonitrile (liquid chromatograph grade)/methanol (liquid chromatograph grade)/ aqueous ammonium acetate (0.05 mol/L) (4:11:5)

		initial	6 days	7 days	14 days	28 days	38 days	90 days	191 days
compound 1	crystal	100		97.2	94.1	87.4			
	MCT[1]	100			101.4		102.1	100.9	
compound 2	crystal	100	84.5		75.0	53.4			
	MCT[2]	100			99.6	98.9			99.6

[1]compound 1/solvent: 0.36 mg/g
[2]compound 2/solvent: 0.12 mg/g

The composition of the present invention causes extremely great enteropooling effect, inhibiting absorption of water in intestines. Further, the present compounds have no or greatly reduced, if any, intestinal contraction effect which PGEs or PGFs may possess. Therefore, the present composition treats constipation without malaise in belly owing to the intestinal contraction, such as bellyache. In addition, the present compound allows constipation to subside effecting normal bowl conditions. Moreover, it requires little time to recover from diarrhea symptoms if caused by the present compounds which possess great promotion effect of intraintestinal transportation. Therefore, they are even very useful as cathartics.

The composition of the present invention can be used as constipation treatment and prevention remedies for animals and humans, and, in general, used for systemic or local applications by oral administration, or as suppository, enema and the like. Sometimes, they may be applied as intravenous or subcutaneous injection. The dosage varies depending on animals, humans, age, weight, conditions, therapeutic effect, administration route, treatment time and the like. Preferably, it is 0.001–1,000 μg/kg, and more preferably 0.01 to 100 μg/kg.

The solid composition for oral administration of the present invention includes tablets, preparations, granules and the like. In such a solid composition, one or more active ingredients may be mixed with at least one inactive diluent, for example, lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinyl pyrrolidone, magnesium aluminate metasilicate and the like. According to the usual work-up, the composition may contain additives other than inactive diluent, for example, lubricant such as magnesium stearate; disintegrant such as fibrous calcium gluconate; stabilizer such as cyclodextrin, for example, α,β- or γ-cyclodextrin; etherified cyclodextrin such as dimethyl-α-, dimethyl-β-, trimethyl-β- or hydroxypropyl-β-cyclodextrin; branched cyclodextrin such as glucosyl-, maltosyl-cyclodextrin; formylated cyclodextrin, cyclodextrin containing sulfur; phospholipid and the like. When the above cyclodextrins are used, inclusion compound with cyclodextrins may be sometimes formed to enhance stability. Alternatively, phospolipid may be sometimes used to form liposome, resulting in enhanced stability.

Tablets or pills may be coated with film soluble in the stomach or intestine such as sugar, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose phthalate as needed. Further, they may be formed as capsules with absorbable substances such as gelatin.

A liquid composition for oral administration may contain pharmaceutically acceptable emulsion, solution, suspension, syrup, elixir as well as generally used inactive diluent. Such composition may contain, in addition to the inactive diluent, adjuvants such as suspensioning agents, sweetening agents, flavoring agents, preservatives, solubilizers, anti-oxidants and the like. The details of the additives may be selected from those described in any general textbooks in the pharmaceutical field. Such liquid compositions may be directly enclosed in soft capsules. However, the selection of a diluent other than those mentioned above, which the bi-cyclic/mono-cyclic compound may be dissolved or admixed in, must carefully be selected so as not to affect the bi-cyclic/mono-cyclic ratio.

Solutions for parenteral administration, for example, suppository, enema and the like according to the present invention include steril, aqueous or non-aqueous solution, suspension, emulsion and the like. The aqueous solution and suspension includes, for example, distilled water, physiological saline and Ringer's solution.

The non-aqueous solution and suspension include, for example, propylene glycol, polyethylene glycol, fatty acid triglyceride, vegetable oil such as olive oil, alcohols such as ethanol, polysorbate and the like. Such composition may contain adjuvants such as preservatives, wetting agent, emulsifier, dispersant, anti-oxidants and the like.

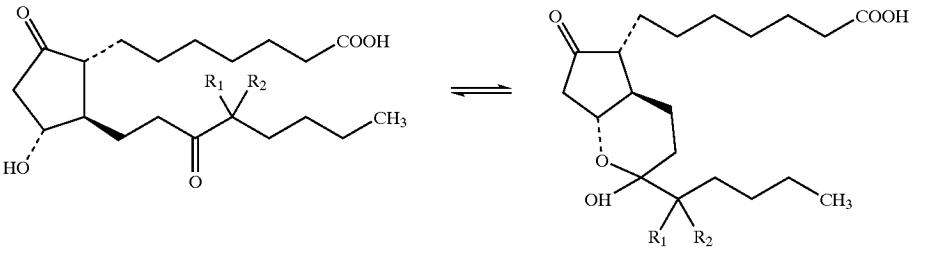
The present invention will be illustrated in the following examples. Which are illustrated by way of example only and not intended to limit the scope of the present invention.

Correlation of Mono-cyclic/bi-cyclic Structure and Biological Activity

To exemplify the effect of halogenated-bi-cyclic compounds with halogen atoms at the C-16 position in the composition of the present invention, the following Examples were prepared and tested.

Example 1

The biological activity of compositions due to the ratios of mono-cyclic/bi-cyclic structures when Z of general formula (I) is an oxygen atom, and a ketone is present at the C-9 position of the present invention can be seen from the following examples. The number of fluorine atoms at the C-16 position and the ratio of mono-cyclic/bi-cyclic structures are shown in Table 1.



Enteropooling tests and diarrhea tests were conducted. The results are set forth in Table 1. The dose that raise the intraintestinal content by 50% was referred to as ED_{50}.

Enteropooling tests and diarrhea tests were conducted. The results are set forth below in Table 2. The dose that raise the intraintestinal content by 50% was referred to as ED_{50}.

TABLE 1

	Example A	Example B	Comparative Example A
Number of F atoms at C-16 position	2	1	0
Ratio of mono-cyclic/bi-cyclic structure*	4:96	1:1	No signal derived from bi-cyclic structure was detected.
Enteropooling activity, ED_{50}	0.6 μg/kg	2 μg/kg	320 μg/kg
Diarrhea in mice	+: at 3 mg/kg (PO[1]) +: at 0.3 mg/kg (SC[2])	±: at 0.3 mg/kg (SC)	−: at 10 mg/kg (PO) −: at 1 mg/kg (SC)

*Determined by NMR measurement in $CDCl_3$ solution.
[1]PO is by mouth (oral administration)
[2]SC is subcutaneous administration

Example 2

The biological activity of the composition due to the ratios of mono-cyclic/bi-cyclic structures when Z in Formula (I) is an oxygen, a ketone is present at the C-9 position, and there is a double bond between the 5,6-carbons is shown below.

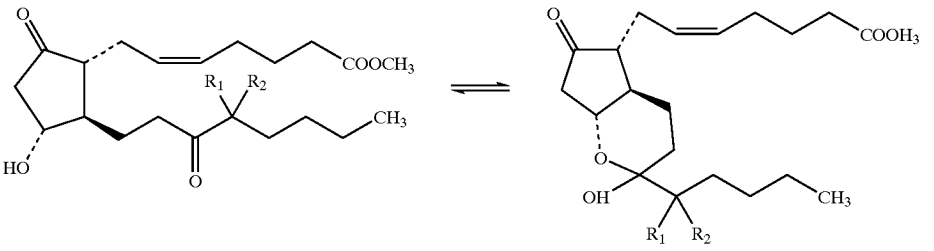


TABLE 2

	Example C	Example D	Comparative Example C
Number of F atoms at C-16 position	2	1	0
Ratio of mono-cyclic/bi-cyclic structure*	4:96	1:1	no signal derived from bi-cyclic structure was detected.
Enteropooling activity, ED_{50}	0.3 μg/kg	3 μg/kg	220 μg/kg

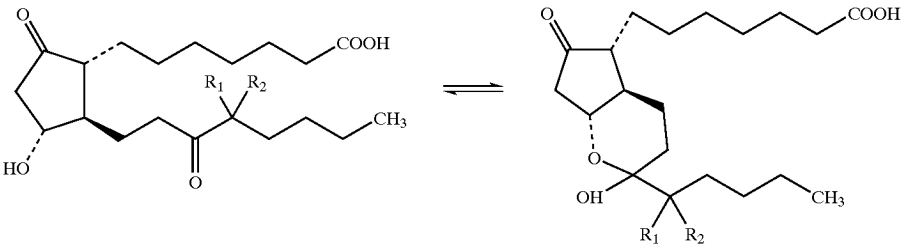
TABLE 2-continued

	Example C	Example D	Comparative Example C
Diarrhea in mice	+: at 1 mg/kg (PO)[1]	−: at 1 mg/kg (PO) +: at 5 mg/kg (PO)	−: at 10 mg/kg (PO)

* Determined by NMR measurement in $CDCl_3$ solution.
[1]PO is by mouth (oral administration)

Effect of the Present Invention Dissolved in Medium Chain Fatty Acid Triglyceride on Bowel Movement After Single Oral Administration to Healthy Male Volunteers

3 to 9 healthy male volunteers were treated with a composition containing the following mono-cyclic/bi-cyclic structures (in $CDCl_3$) in a ratio of 4:96.



The test substance (R_1 and R_2 are F atoms) was dissolved in Panacet 800 (medium chain fatty acid triglyceride manufactured by Nippon Oil & Fat co., Ltd., Amagasaki, Japan) and filled in a capsule (each capsule contains 200 L of the mixture). Each subject was administered one capsule with 100 mL of water.

Table 3 shows the number of subjects who experienced loose stool or diarrhea.

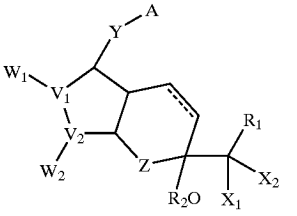
TABLE 3

	Number of Subjects	
Dose	Normal	Loose or Diarrhea
5 μg	1/3	2/3
10 μg	5/7	2/7
20 μg	1/3	2/3
30 μg	2/9	7/9

While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

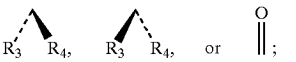
What is claimed is:

1. A method for relieving or preventing constipation in a human constipated patient or cleansing a bowel of a patient which comprises administering to the patient a therapeutically effective amount of the pharmaceutical composition comprising in an amount sufficient for relieving or preventing constipation in a human constipated patient or cleansing a bowel of a human patient a bi-cyclic compound represented by formula (I):



where V_1 and V_2 are carbon atoms;

W_1 and W_2 are



R_3 and R_4 are hydrogen atoms or one of them is OH;

X_1 and X_2 are hydrogen, lower alkyl or halogen atom, and at least one of these is a halogen atom;

Z is an oxygen atom;

R_2 is a hydrogen atom or alkyl;

Y is a saturated or unsaturated $C_{2\text{-}10}$ hydrocarbon chain which is unsubstituted or substituted by oxo, halogen, an alkyl group, hydroxyl or aryl;

A is $-CH_2OH$, $-COCH_2OH$, -COOH or its functional derivative; and

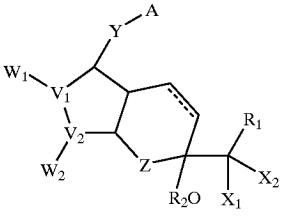
R_1 is a saturated or unsaturated, lower hydrocarbon forming a straight-chain, a branched-chain or a ring, which is unsubstituted or substituted by halogen, oxo, hydroxy, lower alkoxy, lower alkanoyloxy, lower cycloalkyl, lower cycloalkyloxy, aryl, or aryloxy; lower cycloalkyl; lower cycloalkyloxy; aryl or aryloxy,

a bond between C-13 and C-14 position can be a double or single bond, and

C-15 can have a steric configuration of R, S, or a mixture thereof,

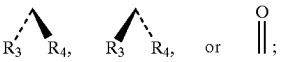
and a compound which is a mono-cyclic tautomer of formula (I), wherein in the composition a ratio of the bi-cyclic compound to the mono-cyclic tautomer is at least 1:1.

2. A method for relieving or preventing constipation in a human constipated patient or cleansing a bowel of a patient which comprises administering to the patient a therapeutically effective amount of the pharmaceutical composition comprising a bi-cyclic compound represented by the following Formula (I);



where V_1 and V_2 are carbon atoms;

W_1 and W_2 are



R_3 and R_4 are hydrogen atoms or one of them is OH;

X_1 and X_2 are hydrogen, lower alkyl or halogen atom, and at least one of these is a halogen atom;

Z is an oxygen atom;

R_2 is a hydrogen atom or alkyl;

Y is a saturated or unsaturated $C_{2\text{-}10}$ hydrocarbon chain which is unsubstituted or substituted by oxo, halogen, an alkyl group, hydroxyl or aryl;

A is $-CH_2OH$, $-COCH_2OH$, -COOH or its functional derivative; and

R_1 is a saturated or unsaturated, lower hydrocarbon forming a straight-chain, a branched-chain or a ring, which is unsubstituted or substituted by halogen, oxo, hydroxy, lower alkoxy, lower alkanoyloxy, lower cycloalkyl, lower cycloalkyloxy, aryl, or aryloxy; lower cycloalkyl; lower cycloalkyloxy; aryl or aryloxy,

a bond between C-13 and C-14 position can be a double or single bond,

C-15 can have a steric configuration of R, S, or a mixture thereof,

a compound which is a mono-cyclic tautomer of formula (I);

and a medium chain fatty acid triglyceride,

wherein in the composition a ratio of the bi-cyclic compound to the monocyclic tautomer is at least 1:1.

3. The method according to claim **1**, wherein in the composition a ratio of bi-cyclic/mono-cyclic structure is at least 20:1.

4. The method according to claim **1**, wherein A is -COOH, W_1 is a ketone, R_2 is a hydrogen atom, and X_1 and X_2 are fluorine atoms.

5. The method according to claim **1**, wherein A is COOH; Y is $(CH_2)_6$; W_1 is =O; R_3 and R_4 are hydrogen atoms; X_1 and X_2 are fluorine atoms; and R_1 is $(CH_2)_3CH_3$.

6. The method according to claims **2**, wherein the ratio of bi-cyclic/mono-cyclic structure is at least 20:1.

7. The method according to claim **2**, wherein A is -COOH, W_1 is a ketone, and X_1 and X_2 are fluorine atoms.

8. The method according to claim **2**, wherein A is COOH; Y is $(CH_2)_6$; W_1 is =O; R_3 and R_4 are hydrogen atoms; X_1 and X_2 are fluorine atoms; and R_1 is $(CH_2)_3CH_3$.

9. The method according to claim **2**, wherein the medium chain fatty acid triglyceride is present in an amount of 1–1,000,000 parts by weight based on one part by weight of the bi-cyclic structure.

10. The method according to claim **9**, wherein the medium chain fatty acid triglyceride is present in an amount of 5–500,000 parts by weight based on one part by weight of the bi-cyclic structure.

11. The method according to claim **9**, wherein the medium chain fatty acid triglyceride is present in an amount of 10–200,000 parts by weight based on one part by weight of the bi-cyclic structure.

12. The method according to claim **2**, wherein the medium chain fatty acid triglyceride is a triglyceride of a fatty acid having 6–14 carbon atoms.

13. The method according to claim **2**, wherein the medium chain fatty acid triglyceride is caprylic acid triglyceride and/or capric triglyceride.

* * * * *

Exhibit B

US008071613B2

(12) **United States Patent**
Ueno

(10) **Patent No.: US 8,071,613 B2**
(45) **Date of Patent: *Dec. 6, 2011**

(54) **ANTI-CONSTIPATION COMPOSITION**

(75) Inventor: **Ryuji Ueno**, Potomac, MD (US)

(73) Assignee: **Sucampo AG**, Zurich (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/142,251**

(22) Filed: **Jun. 2, 2005**

(65) **Prior Publication Data**

US 2005/0222195 A1 Oct. 6, 2005

Related U.S. Application Data

(62) Division of application No. 10/443,046, filed on May 22, 2003, now abandoned, which is a division of application No. 10/138,650, filed on May 6, 2002, now Pat. No. 6,610,732, which is a division of application No. 09/655,760, filed on Sep. 5, 2000, now Pat. No. 6,414,016.

(51) **Int. Cl.**
A61K 31/44 (2006.01)
A61K 31/34 (2006.01)

(52) **U.S. Cl.** **514/300**; 514/302; 514/469

(58) **Field of Classification Search** 514/302, 514/469

See application file for complete search history.

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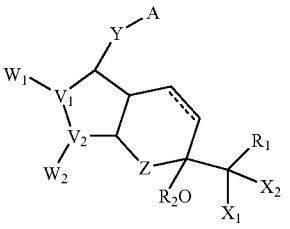
Primary Examiner — Brandon Fetterolf
Assistant Examiner — Shirley V Gembeh
(74) *Attorney, Agent, or Firm* — Sughrue Mion, PLLC

(57) **ABSTRACT**

An object of the present invention is to provide an anti-constipation composition containing a halogenated-bi-cyclic compound as an active ingredient in a ratio of bi-cyclic/mono-cyclic structure of at least 1:1. The halogenated-bi-cyclic compound is represented by Formula (I):



where X_1 and X_2 are preferably both fluorine atoms. The composition can be used to treat constipation without substantive side-effects, such as stomachache.

26 Claims, No Drawings

ANTI-CONSTIPATION COMPOSITION

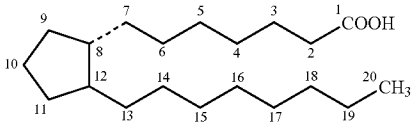
This is a request for a Divisional Application of prior application Ser. No. 10/443,046 filed May 22, 2003, now abandoned which is a divisional of U.S. application Ser. No. 10/138,650 filed May 6, 2002, now U.S. Pat. No. 6,610,732, which is a divisional of U.S. application Ser. No. 09/655,760 filed Sep. 5, 2000, now U.S. Pat. No. 6,414,016; the disclosures of which are incorporated herein by reference.

TECHNICAL FIELD

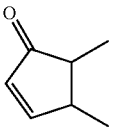
The present invention relates to a novel therapeutic composition that contains halogenated bi-cyclic structures for treatment of constipation and use thereof.

BACKGROUND OF THE INVENTION

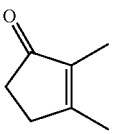
Prostaglandins (hereinafter referred to as PGs) is the name of the group of fatty acids which possess various physiological activities and contained in human and animal tissues and organs. PGs basically contain the prostanoic acid skeleton of the following formula:



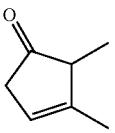
and some synthetic products may contain the above skeleton with some modification. PGs are classified into several types according to the structure and substituents on the five-membered ring, for example,



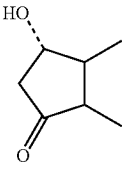
Prostaglandins of the A series (PGAs);



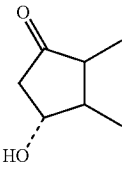
Prostaglandins of the B series (PGBs);



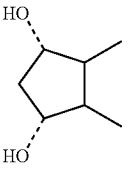
Prostaglandins of the C series (PGCs);



Prostaglandins of the D series (PGDs);

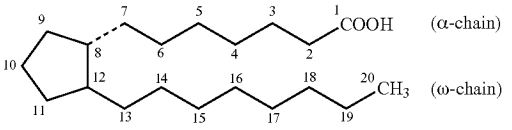


Prostaglandins of the E series (PGEs);



Prostaglandins of the F series (PGFs);
and the like. Further, they are classified into PG_1s containing a 13,14-double bond; PG_2s containing, 5,6- and 13,14-double bonds; and PG_3s containing 5,6-, 13, 14- and 17,18-double bonds.

PGs are expressed as follows. In PGs, the carbons constituting an α-chain, an ω-chain and a five-membered ring are numbered according to the basic skeleton as follows:



That is, in the basic skeleton, the constituent carbon atoms are numbered in such a way that the carbon atom in the carboxyl group is C-1, and the α-chain contains C-2-C-7, the number increasing toward the ring, the five-membered ring contains C-8-C-12, and the ω-chain contains C-13-C-20. When the carbons of α-chain are fewer, the numbers of the carbon atoms ensuing C-2 should be properly shifted, and when more than 7, the compound is named provided that carbon at the C-2 position has substituent instead of carboxyl group (at the C-1 position). When the ω-chain contains fewer carbon atoms they should be numbered correspondingly smaller than 20, and when more than 8, the carbon atoms at the 21 position and thereafter should be regarded as a substituent. As configuration, it is considered according to that of the above essential skeleton unless otherwise described.

For example, PGD, PGE and PGF mean compounds having hydroxyl group at the C-9 and/or C-11 positions. In the present invention, PGs also include those having other group instead of the hydroxyl group on the C-9 and/or C-11 positions, they being named as 9-dehydroxy-9-substituted or 11-dehydroxy-11-substituted compounds.

In addition, PGs may include the isomers, such as bi-cyclic tautomers, optical isomers; geometrical isomers, or the like.

PGs are known to have various pharmacological and physiological activities, for example, vasodilation, inducing of inflammation, platelet aggregation, stimulating uterine muscle, stimulating intestinal muscle, anti-ulcer effect and the like. PGEs or PGFs are found to possess contraction of intestines caused by intestinal stimulation is great, while enteropooling effect is poor. Accordingly, it is impossible to use PGEs or PGFs as cathartics because of side effects such as stomachache caused by the intestinal contraction.

On the other hand, PGs having a 13,14-single bond and a C-15 constituting carbonyl group, and those having a 13,14-double bond and a C-15 constituting carbonyl group are found to exist in human or animal metabolites. These 13,14-dihydro-15-keto-prostaglandins and 15-keto-prostaglandins (hereinafter referred to as 15-keto-PGs) are known to be naturally produced metabolites by enzymatic metabolism of the corresponding PGs in vivo. These 15-keto-PGs have been reported to hardly exhibit various physiological activities that PGs possess and be pharmacologically and physiologically inactive metabolites [see, Acta Physiologica Scandinavica, 66, p. 509-(1966)].

U.S. Pat. No. 5,317,032 to Ueno et al. describes prostaglandin cathartics, including the existence of bi-cyclic tautomers. However, the pronounced activity as anti-constipation treatment and prevention agents of the bi-cyclic tautomers has not been heretofore known.

While estimating the pharmacological activities of the analogues of 15-keto-PGs, however, the present inventors have found that the corresponding bi-cyclic compounds, i.e., the bi-cyclic tautomers, substituted by one or more halogen atoms can be employed in small doses for relieving constipation. At the C-16 position, especially, fluorine atoms, can be employed in small doses for relieving constipation. Where desired, larger doses to cause strong cathartic effect can be employed, although the primary purpose of the present invention is to restore a normal number of bowel movements (3 to 7 per week).

SUMMARY OF THE INVENTION

An object of the present invention is to provide a composition for treatment of constipation comprising bi-cyclic-halogenated compounds without substantive side effects such as stomachache caused by intestinal contraction. Accordingly, the bi-cyclic-halogenated compounds of the present invention may be used not only for treatment of chronic or intermittent constipation, but also for treatment or prevention of constipation (as well as to effect loose bowels when desired) in the patients suffering from constipation associated with, for example, in hernia or cardiovascular system disease, in order not to strain at stool, or suffering from proctogenic diseases. Moreover, they may be used to produce normal bowel movements for washing out harmful substances from intestine in case of drug or food poisoning. Additionally, the bi-cyclic halogenated compounds may be used as a bowel cleansing agent used for preparation of the bowel prior to preventative, diagnostic or surgical procedures.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an anti-constipation composition (prevention and/or treatment of constipation)containing bi-cyclic-halogenated compounds as active ingredients.

Cathartics work by the combination of one or more of the four mechanisms shown below, thereby increasing water content of feces and promoting transfer of the content in the intestines:

(i) Water and electrolytes may be kept in intestines owing to the hydrophilicity or osmotic pressure of the drug, thereby the intraintestinal content increased in volume which indirectly results in faster transfer thereof.

(ii) The drug may work on the intestinal mucosa to reduce total amount of normal absorption of electrolytes and water and increase the amount of water, indirectly resulting in faster transfer of the intraintestinal content.

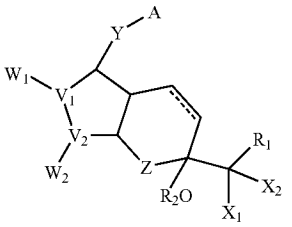
(iii) The drug may work on the intestinal mucosa to increase total amount of normal secretion of electrolytes and water and increase the amount of water, directly and/or indirectly resulting in faster transfer of the intraintestinal content.

(iv) The drug firstly works on intestinal movement to fasten transfer, indirectly resulting in reduced net absorption of water and electrolytes because the time for them to be absorbed is reduced.

The enteropooling test employed in the present invention is intended to investigate mainly on the action (ii) and/or (iii), which assesses the effect of the drug on the intraintestinal water pool by measuring the volume of the intraintestinal content. The bi-cyclic-halogenated compounds of the present invention may show extremely great enteropooling effect. However, they hardly or slightly cause contraction of intestines which is one of indexes for assessment of the action (iv). Accordingly, the bi-cyclic-halogenated compounds of the present invention are considered to alleviate constipation by mainly acting on intestinal mucosa directly or indirectly to affect transfer of electrolytes and water from intestinal walls into blood vessels and/or from blood vessels into intestines, resulting in reduced water absorption and/or in increased water secretion through the intestines, increased intraintestinal water pool and promoted transfer of the intraintestinal content.

A preferred compound used in the present invention is represented by formula (I):

Formula (I)



where V_1 and V_2 are carbon or oxygen atoms;

W_1 and W_2 are

;

R_3 and R_4 are both hydrogen atoms or one of them is OH;

X_1 and X_2 are hydrogen, lower alkyl or halogen atom, and at least one of these is a halogen atom;

Z is a carbon, oxygen, sulfur or nitrogen atom;

R_2 is a hydrogen atom or lower alkyl;

Y is a saturated or unsaturated $C_{2\text{-}10}$ hydrocarbon chain which is unsubstituted or substituted by oxo, halogen, an alkyl group, hydroxyl or aryl;

A is —CH_2OH, —$COCH_2OH$, —COOH or its functional derivative; and

R_1 is a saturated or unsaturated, lower hydrocarbon forming a straight-chain, a branched-chain or a ring, which is unsubstituted or substituted by halogen, oxo, hydroxy, lower alkoxy, lower alkanoyloxy, lower cycloalkyl, lower cycloalkyloxy, aryl, or aryloxy. Preferably R_1 is not substituted. Where a substituent is present, care must be exercised

to avoid possible steric hinderance in formation of the bi-cyclic compound from or in association with the corresponding mono-cyclic PGs.

The steric configuration of C-15 can be R, S, or a mixture thereof.

The bond between C-13 and C-14 position can be a single or double bond.

In the above formula, the term "unsaturated" is intended to include at least one or more double bonds and/or triple bonds that are isolatedly, separately, or serially present between the carbon atoms of the main and/or side chains. An unsaturated bond between two serial positions is represented by denoting the lower number of the two positions, and an unsaturated bond between two distal positions is represented by denoting both of the positions. Preferred unsaturated bonds are a double at position 2 and a double or triple bond at position 5.

The term "lower" is intended to include a group having 1 to 8 carbon atoms, unless otherwise specified.

The term "ring" includes lower cycloalkyl, lower cycloalkoxy, aryl or aryloxy.

The term "halogen" includes fluorine, chlorine, bromine, or iodine atom. Particularly preferable is a fluorine atom.

The term "lower alkoxy" refers to a group of lower alkyl-O—, wherein lower alkyl is a straight or branched chain saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methyl, ethyl, propyl, isopropyl, buyl, isobutyl, t-butyl, pentyl and hexyl.

The term "hydroxy(lower)alkyl" refers to a lower alkyl as defined above which is substituted with at least one hydroxy group such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 1-methyl-1-hydroxyethyl.

The term "lower alkanoyloxy" refers to a group represented by the formula RCO—O—, wherein RCO— is an acyl group formed by oxidation of a lower alkyl group as defined above, such as acetyl.

The term "lower cycloalkyl" refers to a cyclic group formed by cyclization of a lower alkyl group as defined above but contains three or more carbon atoms, and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "lower cycloalkyloxy" refers to the group of lower-cycloalkyl-O—, wherein lower cycloalkyl is as defined above.

The term "aryl" may include unsubstituted or substituted aromatic carbocyclic or heterocyclic groups (preferably mono-cyclic groups), for example, phenyl, naphthyl, tolyl, xylyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, furzanyl, pyranyl, pyridyl, pyridazyl, pyrimidryl, pyrazyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidino, piperazinyl, morpholono, indolyl, benzothienyl, quinolyl, isoquinolyl, puryl, quinazolinyl, carbazolyl, acridinyl, phenathridinyl, benzimidazolyl, benzimidazolonyl, benzothiazolyl and phenothiazinyl. Examples of substituents are halogen atom and halo (lower)alkyl, wherein halogen atom and lower alkyl are as defined above.

The term "aryloxy" refers to a group represented by the formula Ar—O, wherein Ar is aryl as defined above.

The bi-cyclic-16-halogen compounds used in the present invention may be salts or those with an esterified carboxyl group or etherified group. Such salts include pharmaceutically acceptable salts, for example, those of alkali metals such as sodium, potassium; those of alkaline earth metals such as calcium, magnesium; those of physiologically acceptable ammonium salts such as ammonia, methylamine, dimethylamine, cyclopentylamine, cyclohexylamine, benzylamine, piperidine, ethylenediamine, monoethanolamine, diethanolamine, triethanolamine, monomethylmonoethanolamine, trometamine, lysine, procaine, caffeine, arginine, tetralkylammonium salt and the like. These salts may be prepared by a conventional process, for example, from the corresponding acid and base or by salt interchange.

Such esters and ethers include, for example, straight or branched alkyl esters and ethers which may contain one or more unsaturated bonds such as methyl, ethyl, propyl, butyl, isopropyl, isobutyl, t-butyl, pentyl, 2-ethylhexyl; those having an alicyclic group such as a cyclopropyl, cyclopentyl or cyclohexyl group; those containing an aromatic group such as a benzyl or phenyl group (wherein the aromatic group may contain one or more substituents); a lower alkenyl such as ethynyl and propynyl, hydroxyalkyl or alkoxyalkyl such as hydroxyethyl, hydroxyisopropyl, polyhydroxyethyl, polyhydroxyisopropyl, methoxyethyl, ethoxyethyl or methoxyisopropyl ester or ether; optionally substituted aryls such as phenyl, tosyl, t-butylphenyl, salicyl, 3,4-di-methoxyphenyl and benzamidophenyl; alkylsilyls such as a trimethylsilyl or triethylsilyl; or a tetrahydropyranyl ester or ether.

Preferred esters and ethers include, for example, straight-chain or branched lower alkyl such as methyl, ethyl, propyl, n-butyl, isopropyl or t-butyl; a benzyl; or hydroxyalkyl such as a hydroxyethyl or hydroxyisopropyl.

Preferred A is —COOH or its pharmaceutically acceptable salt or ester.

Preferred X_1 and X_2 are both being halogen atoms, and more preferably, fluorine atoms.

Preferred W_1 is =O.

Preferred W_2 is where R_3 and R_4 are both hydrogen atoms.

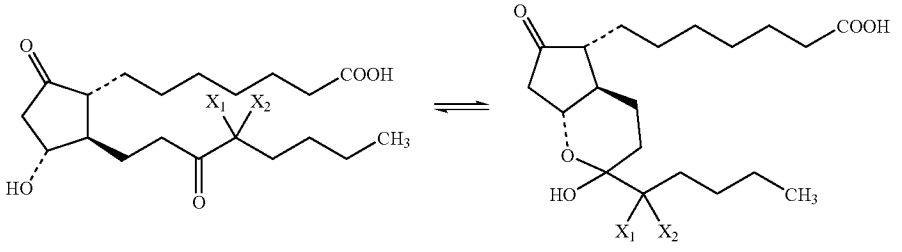
Preferred Z is an oxygen atom.

Preferred Y is an unsubstituted saturated or unsaturated hydrocarbon chain having 6-8 carbon atoms.

Preferred R_1 is an unsubstituted saturated or unsaturated hydrocarbon chain having 4-8 carbon atoms.

R_2 is preferably a hydrogen atom.

The composition of the present invention may include the isomers of the above compounds. Examples of such isomers include mono-cyclic tautomers having a keto group at the C-15 position and halogen at the C-16 position; optical isomers; geometrical isomers and the like.



Tautomer I Tautomer II

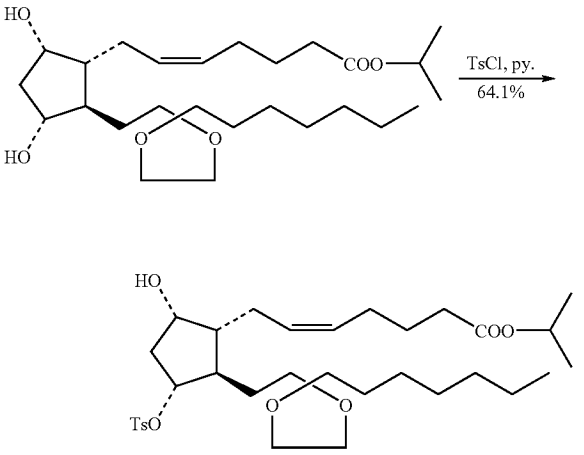
The tautomerism between the oxygen atom at the C-11 position and the keto group at the C-15 position, shown above, is especially significant in the case of compounds having a 13,14-single bond and two fluorine atoms at the C-16 position.

It has been discovered that in the absence of water, compounds represented by Formula (I) exist predominantly in the form of the bi-cyclic compound. In aqueous media, it is believed that hydrogen bonding occurs between, for example, the ketone position at the C-15 position, thereby hindering bi-cyclic ring formation. In addition, it is believed that the halogen atom(s) at the C-16 position promote bi-cyclic ring formation. The mono-cyclic/bi-cyclic structures, for example, may be present in a ratio of 1:6 in D_2O; 1:10 in CD_3OD-D_2O and 4:96 in $CDCl_3$. Accordingly, a preferable embodiment of the present invention is the composition in which the bi-cyclic form is present in ratio of bi -cyclic/mono-cyclic of least 1:1, and preferably 20:1, or even greater to substantially all bi-cyclic compound; 100% bi-cyclic compound is within this invention.

The above described bi-cyclic-16-halogen compound may prepared according to the general process set forth below:

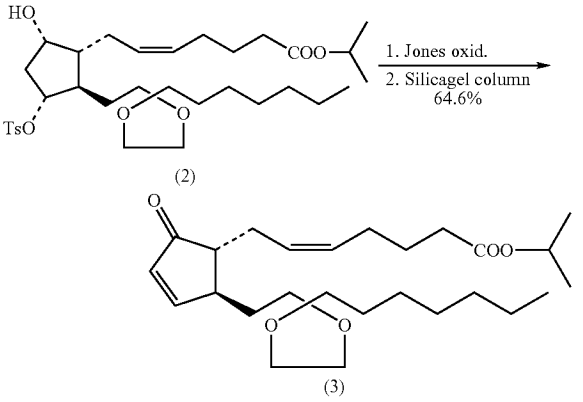
Preparation of Isopropyl 7-[(1S,3S,6S,7R)-3-heptyl-3-hydroxy-bicyclo[4.3.0]nonane-8-one-7-yl]hept-5-enoate and Isopropyl 7-[1S,3R,6S,7R)-3-heptyl-3-hydroxy-bicyclo[4.3.0]nonane-8-one-7-yl]hept-5-enoate

1. Preparation of Isopropyl (Z)-7-[1R,2R,3R,5S)-2-(3,3-ethylenedioxydecyl)-5-hydroxy-3-(p-toluensulfonyl)cyclopentyl]hept-5-enoate (2)



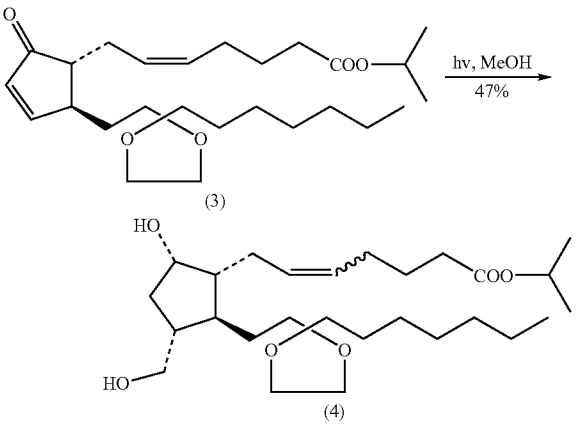
To a mixture of pyridine (0.77 g) and isopropyl(Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3,3-ethylenedioxydecyl)cyclopentyl]hept-5-enoate (1) (4.05 g) in dichloromethane, a solution of tosyl chloride (1.86 g) in dichloromethane was added at 0° C., and stirred for 2 days at the temperature. During the reaction, each tosyl chloride (5.58 g) and pyridine (2.31 g) was added in three portions. After the usual work-up, the crude product was chromatographed on silica gel to give isopropyl (Z)-7-[(1R,2R,3R,5S)-2-(3,3-ethylenedioxydecyl)-5-hydroxy-3-(p-toluenesulfoxy)cyclopentyl]hept-5-enoate (2). Yield 3.45 g, 64.1%.

2. Preparation of Isopropyl (Z)-7-[(1R,2S)-2-(3,3-ethylenedioxydecyl)-5-oxocyclopent-3-enyl]hept-5-enoate (3)



Isopropyl (Z)-[1R,2R,3R, 5S)-2-(3,3-ethylenedioxydecyl)-5-hydroxy-3-(p-toluenesulfoxy)cyclopentyl]hept-5-enoate (2) (1.72 g) was oxidized in acetone at −40° C. to −20° C. with Jones reagent for 4 hours. After the usual work-up, the crude product was passed through silica gel pad with n-hexane/ethyl acetate (3.5/1). The product was further chromatographed on silica gel (n-hexane/ethyl acetate=4/1). Isopropyl (Z)-7-[(1R,2S)-2-(3,3-ethylenedioxydecyl)-5-oxo-cyclopent-3-enyl]hept-5-enoate (3) was obtained. Yield 0.81 g, 64.6%.

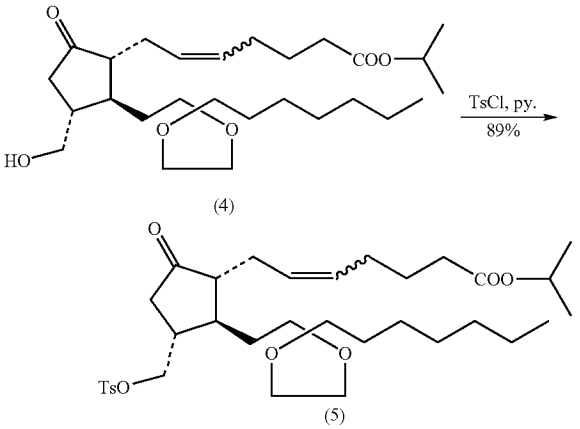
3. Preparation of Isopropyl-7-[(1R,2S,3R)-2-(3,3-ethylenedioxydecyl)-3-hydroxymethyl-5-oxocyclopentyl]hept-5-enoate (4)



Isopropyl (Z)-7-[(1R,2S)-2-(3,3-ethylenedioxydecyl)-5-oxo-cyclopent-3-enyl]hept-5-enoate (3) (0.81 g) and benzophenone were dissolved in methanol. Under argon atmosphere, the solution was irradiated with 300-W high-pressure mercury lamp for 4 hours and 40 minutes. After evaporation of the solvent, the crude product was chromatographed on silica gel (n-hexane/ethyl acetate=3/2) to give isopropyl-7-

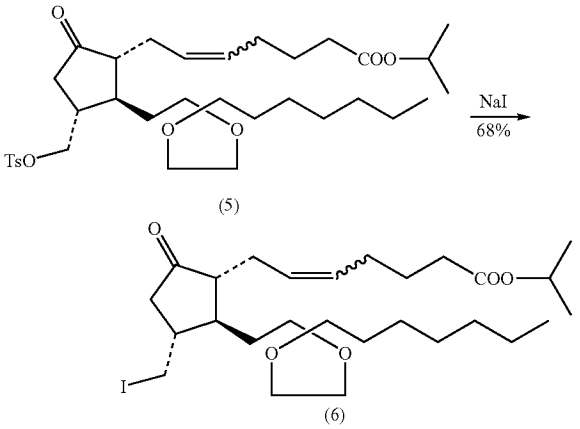
[(1R,2S,3 R)-2-(3,3-ethylenedioxydecyl)-3-hydroxymethyl-5-oxocyclopentyl]hept-5-enoate (4). Yield 0.41 g, 47%.

4. Preparation of Isopropyl-7-[1R,2S,3R)-2-(3,3-ethylenedioxydecyl)-5-oxo-3-(p-toluenesulfoxymethyl)cyclopentyl]hept-5-enoate (5)



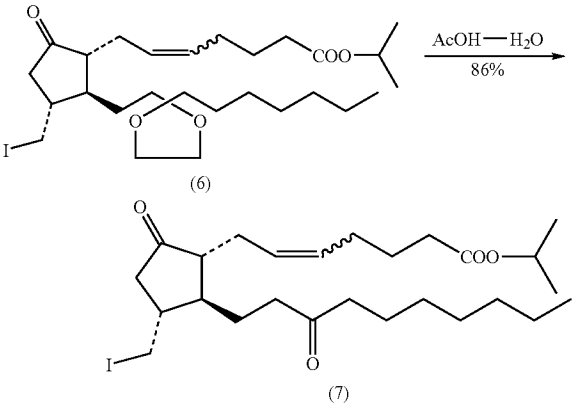
Isopropyl-(1R,2S,3R)-2-(3,3-ethylenedioxydecyl)-3-hydroxymethyl-5-oxocyclopentyl]hept-5-enoate (4) (0.21 g) and pyridine (0.07 g) were dissolved in dichloromethane. To this solution, tosyl chloride (0.17 g) was added at 0° C., and the mixture was stirred for 72 hours. After the usual work-up, the crude product was chromatographed on silica gel to give isopropyl 7-(1R,2S,3R)-2-(3,3-ethylenedioxydecyl)-5-oxo-3-(p-toluenesulfoxy)methylcyclopentyl]hept-5-enoate (5). Yield 0.25 g, 89%.

5. Preparation of Isopropyl-7-[(1R,2R,3R)-2-(3,3-ethylenedioxydecyl)-3-iodemethyl-5-oxocyclopentyl]hept-5-enoate (6)



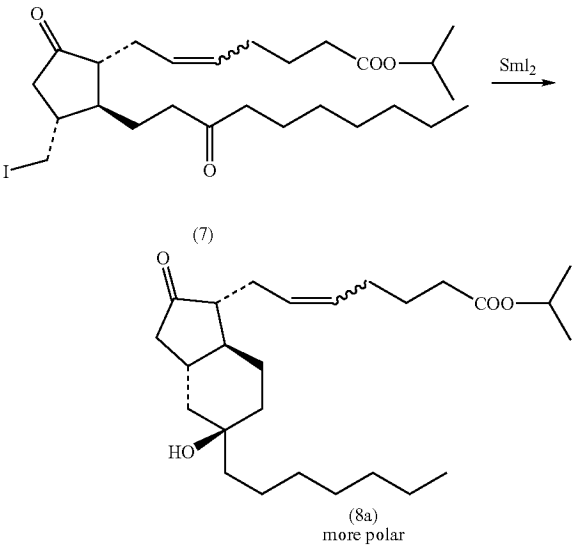
Isopropyl 7-(1R,2S,3R)-2-(3,3-ethylenedioxydecyl)-5-oxo-3-(p-toluenesulfoxy)methylcyclopentyl]hept-5-enoate (5) (0.25 g) was dissolved in acetone, and sodium iodide (0.12 g) was added. The mixture was refluxed for 3 hours. Sodium iodide (0.097 g) was added to the mixture, and the mixture was refluxed for additional 80 minutes. After the usual work-up, the crude product was chromatographed on silica gel (n-hexane/ethyl acetate=5/1) to give isopropyl 7-(1R,2R,3R)-2-(3,3-ethylenedioxydecyl)-3-iodemethyl-5-oxocyclopentyl]hept-5-enoate (6). Yield 0.16 g, 68%.

6. Preparation of Isopropyl 7-(1R,2R,3R)-3-iodemethyl-5-oxo-2-(3-oxodecyl)cyclopentyl]hept-5-enoate (7)



Isopropyl 7-(1R,2R,3 R)-2-(3,3-ethylenedioxydecyl)-3-iodemethyl-5-oxocyclopentyl]hept-5-enoate (6) (0.16 g) was dissolved in a mixed solvent of acetic acid/water/tetrahydrofuran (3/1/1). The mixture was stirred for 20 hours at room temperature and for 2.5 hours at 50° C. After evaporation of the solvent, the obtained residue was chromatographed on silica gel (n-hexane/ethyl acetate=1/1) to give isopropyl 7-(1R,2R,3R)-3-iodemethyl-5-oxo-2-(3-oxodecyl)cyclopentyl]hept-5-enoate (7). Yield. 0.13 g; 86%.

7. Preparation of Isopropyl 7-(1S,3S,6S,7R)-3-heptyl-3-hydroxy-bicyclo[4.3.0]nonane-8-one-7-yl]hept-5-enoate (8a) and Isopropyl 7-(1S,3R,6S,7R)-3-heptyl-3-hydroxy-bicyclo[4.3.0]nonane-8-one-7-yl]hept-5-enoate (8b)



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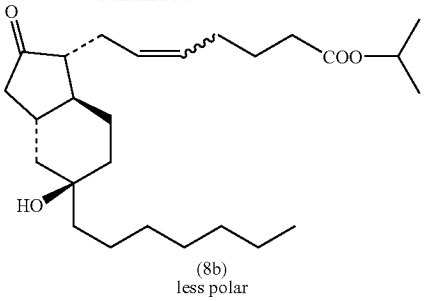


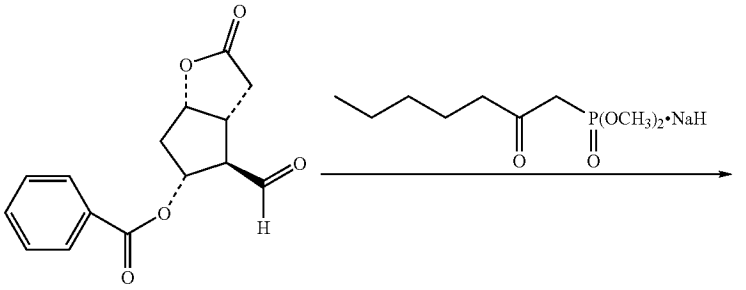
(8b)
less polar

Isopropyl 7-(1R,2R,3R)-3-iodemethyl-2-(3-oxodecyl)-5-oxocyclopentyl]hept-5-enoate (7) (0.0574 g) and zirconocene dichloride were dissolved in tetrahydrofuran. The

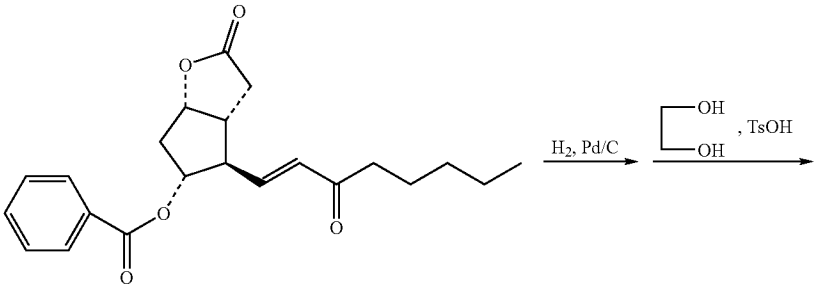
mixture was sonicated under argon stream to purge the air out from the mixture. To the mixture samarium iodide in tetrahydrofuran (0.1 M, 2.1 mL) was added dropwise. The mixture was stirred for 30 minutes at room temperature, and then hydrochloric acid (0.1M, 1 mL) was added. After the usual work-up, the crude product was chromatographed on silica gel (n-hexane/ethyl acetate=5/1). Two bicyclic products, more polar (8a) and its epimer, less polar (8b) and starting material (7) were obtained as follows:

Isopropyl 7-(1S,3S,6S,7R)-3-heptyl-3-hydroxy-bicyclo[4.3.0]nonane-8-one-7-yl]hept-5-enoate (8a) and Isopropyl 7-(1S,3R,6S,7R)-3-heptyl-3-hydroxy-bicyclo[4.3.0]nonane-8-one-7-yl]hept-5-enoate (8b): Yield 8(a) 5.1 mg, Yield 8(b) 7.2 mg, Recovery of starting material (7) 26.7 mg.

A theoretical synthesis for a compound represented by Formula (I) where Z is a sulfur atom and W_1 is an —OH group is set forth below.



[1]



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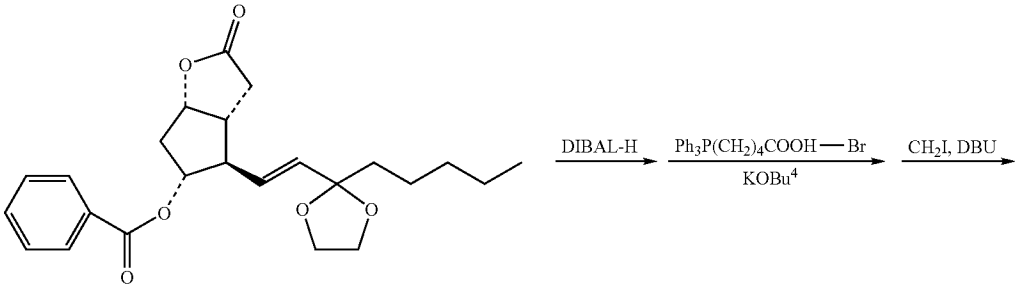

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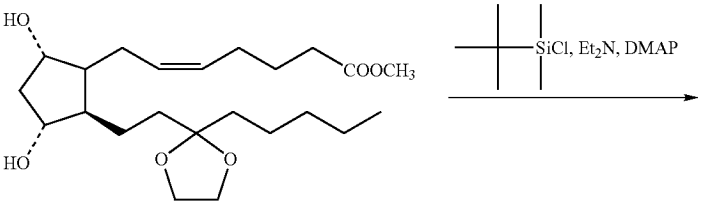

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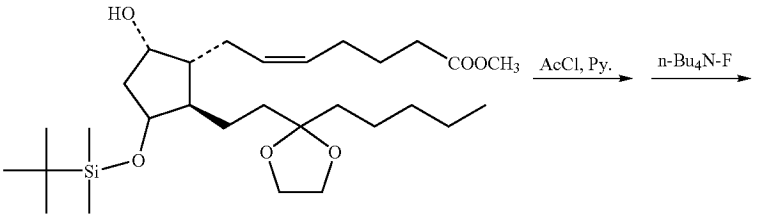

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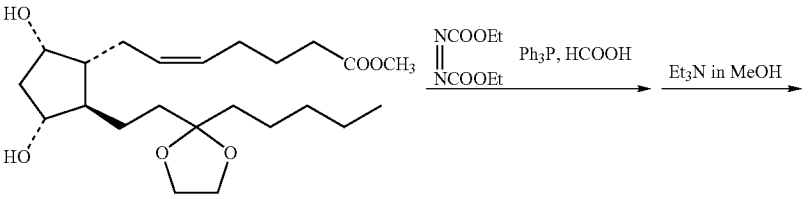

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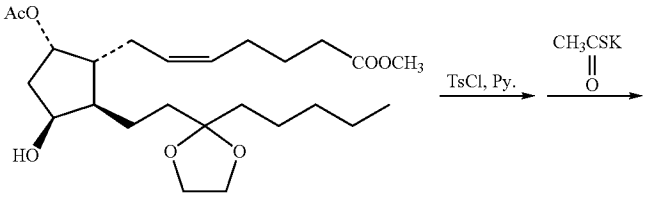

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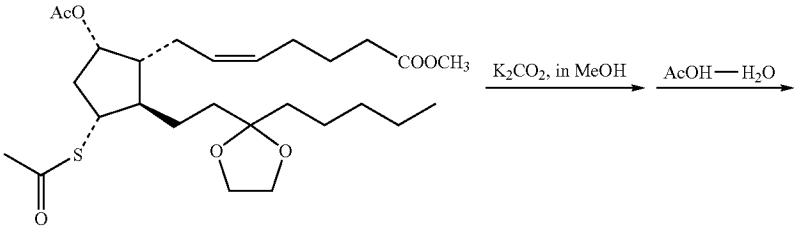

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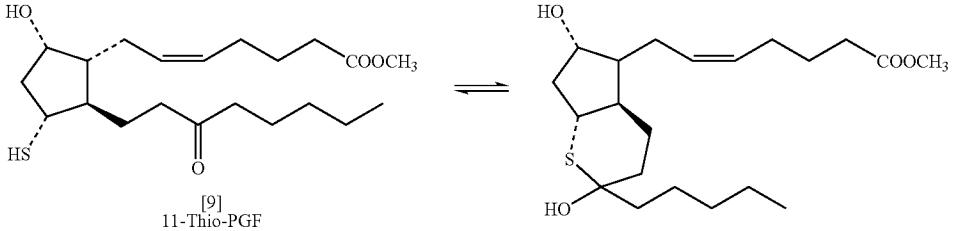
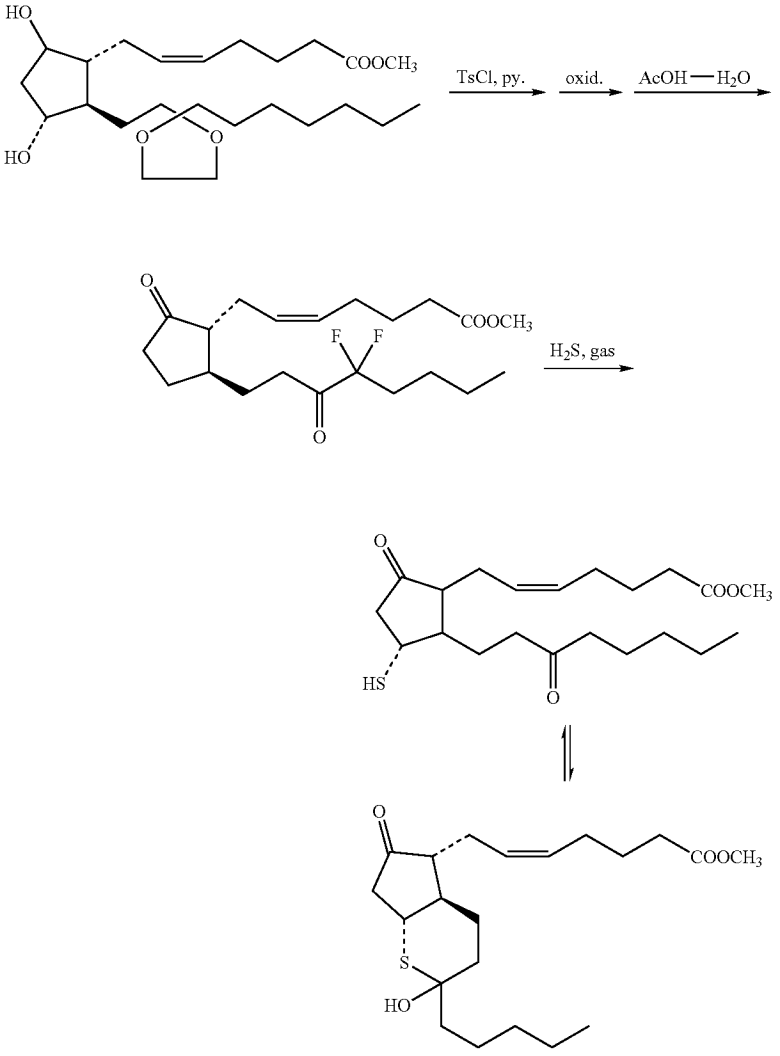


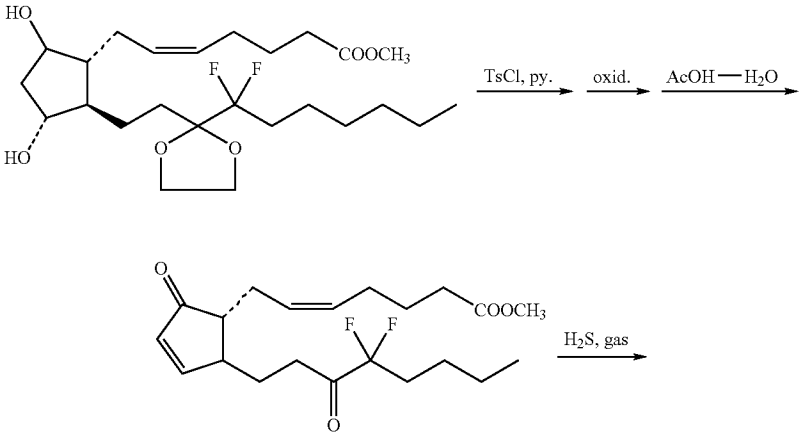
[9]
11-Thio-PGF

n-Bu4N-F: tetrabutylammonium fluoride
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H: diisobutylaluminum hydride
DMAP: 4-dimethylaminopyridine
NaBH4: sodium borohydride

A theoretical synthesis for a compound represented by Formula (I) where Z is a sulfur atom and W_1 is a keto is set forth below:



A theoretical synthesis for a compound represented by Formula (I) where Z is a sulfur atom, W_1 is a keto and X_1 and X_2 are fluorine atoms is set forth below:



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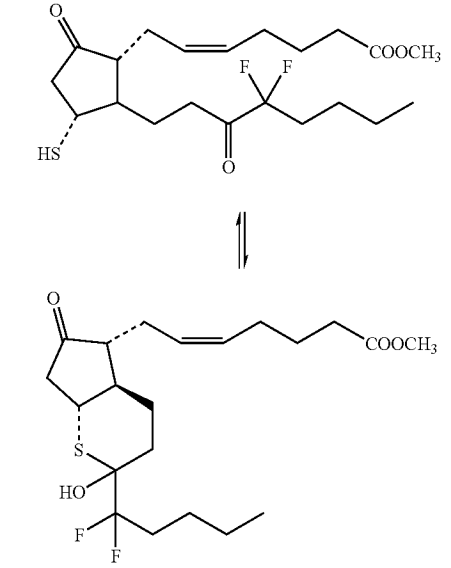
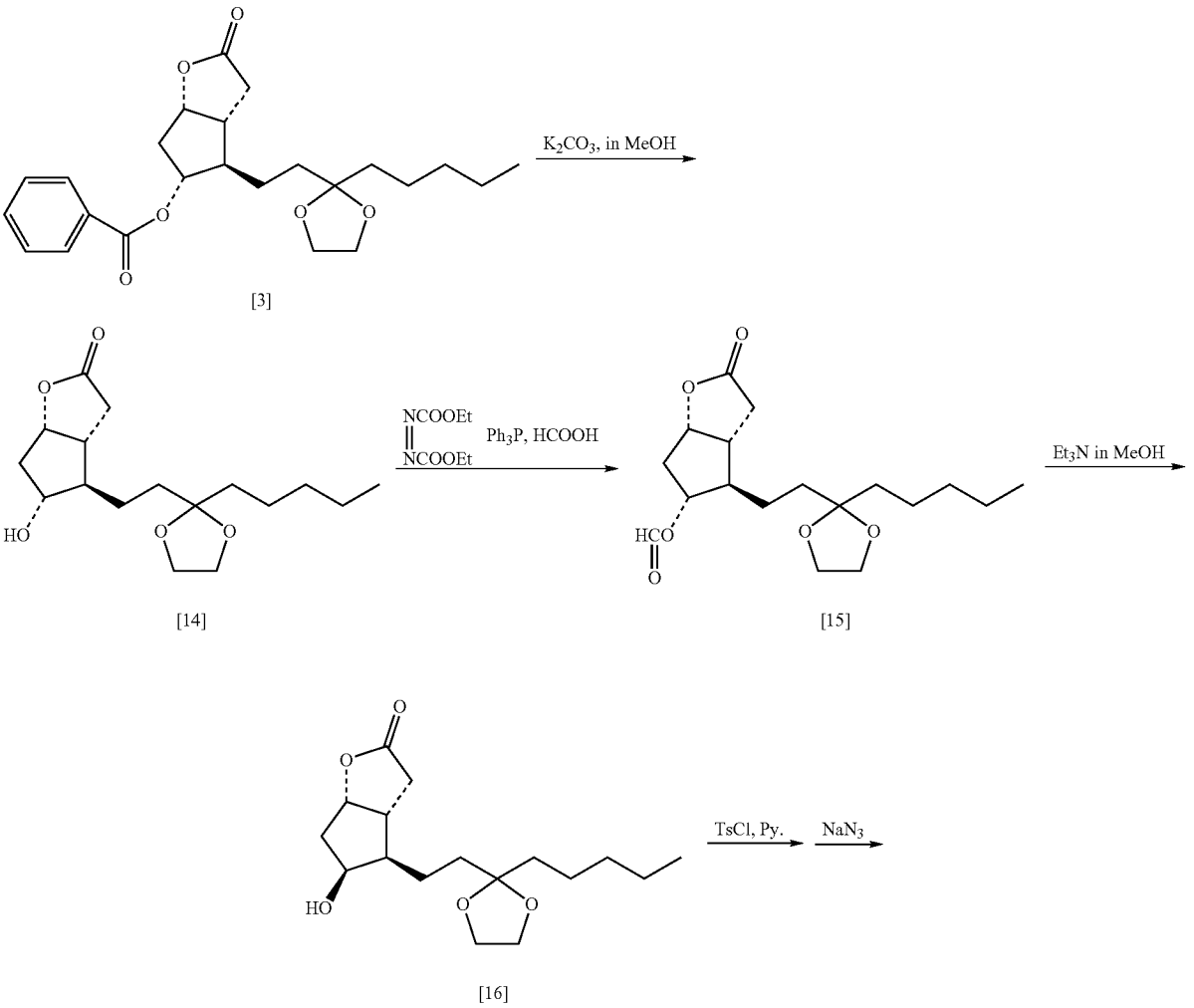


A theoretical synthesis for a compound represented by Formula (I) where Z is a nitrogen atom is set forth below:



[3]

[14]

[15]

[16]

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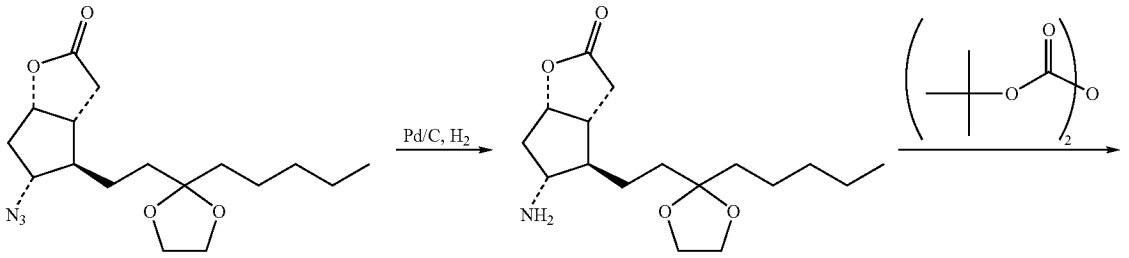
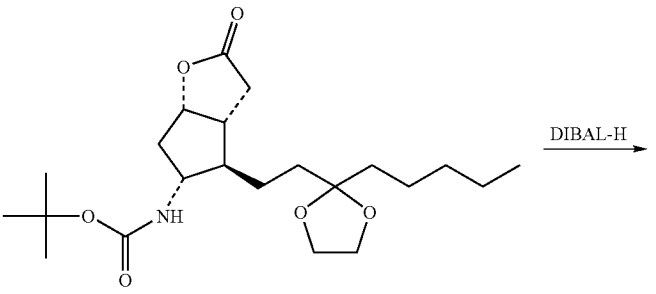


[17] [18]



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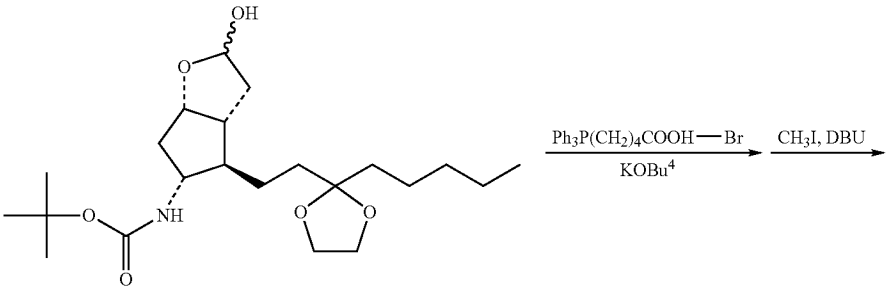

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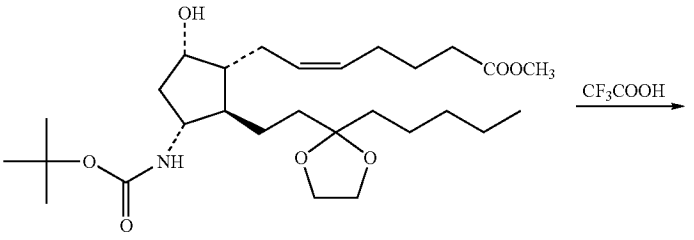

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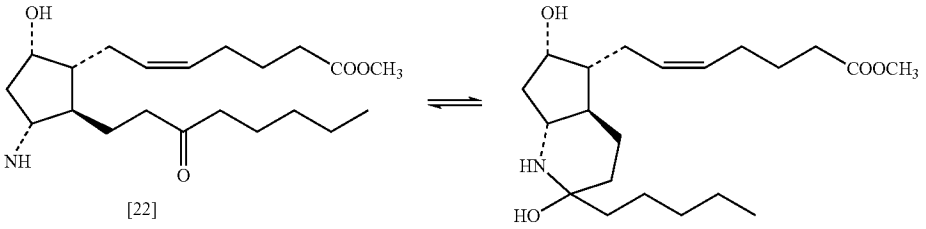
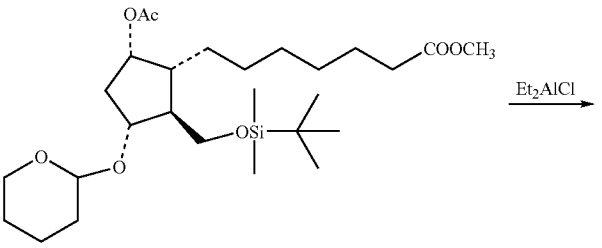


[22] [23]

Another theoretical synthesis of a compound represented by Formula (I) where Z is a nitrogen atom is set forth below:



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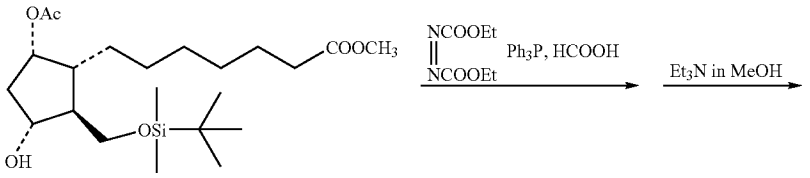

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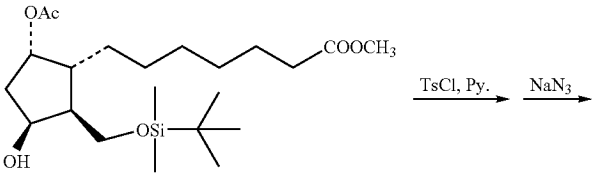

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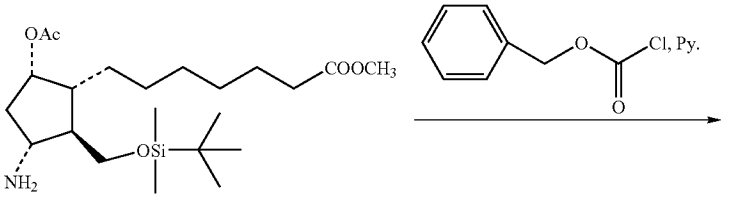

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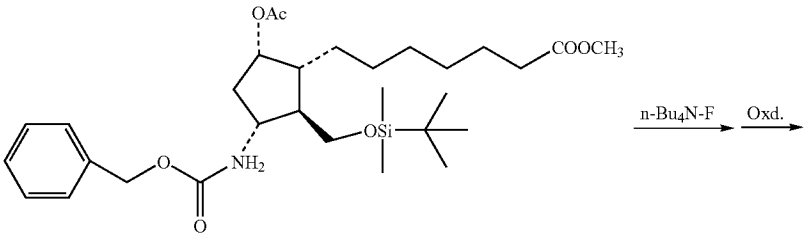

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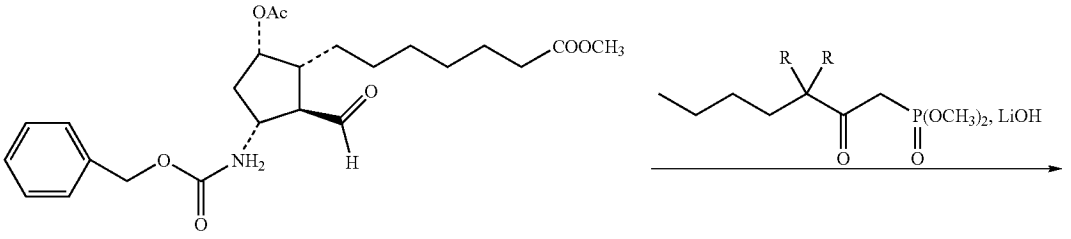

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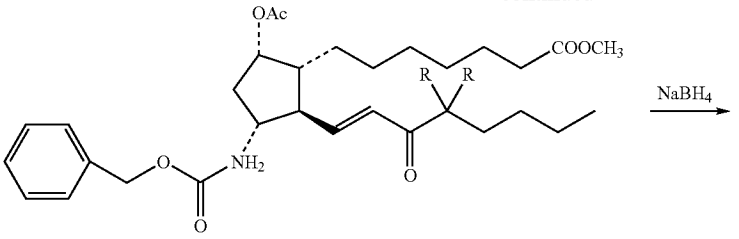

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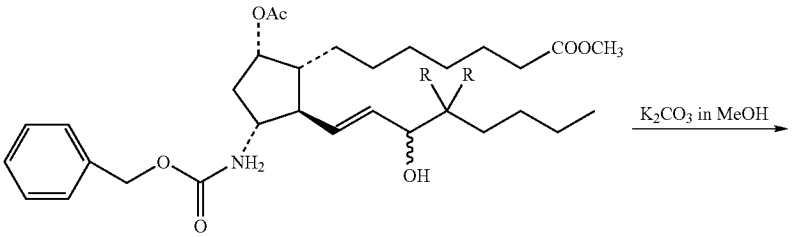

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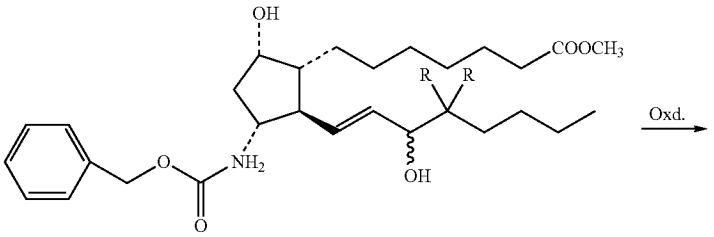

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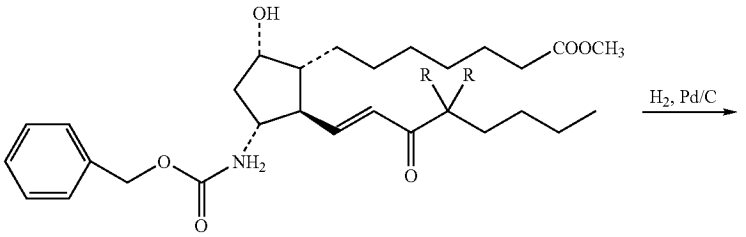

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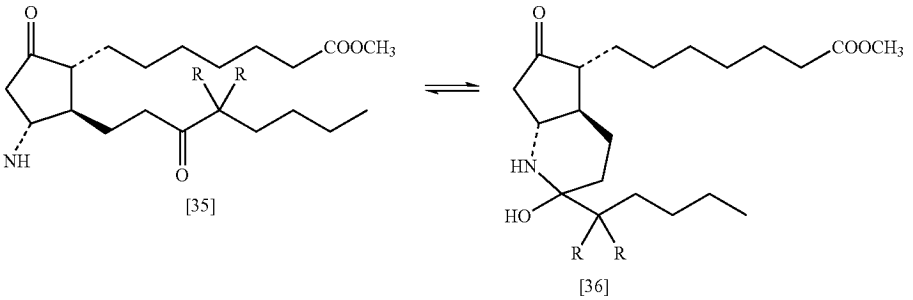


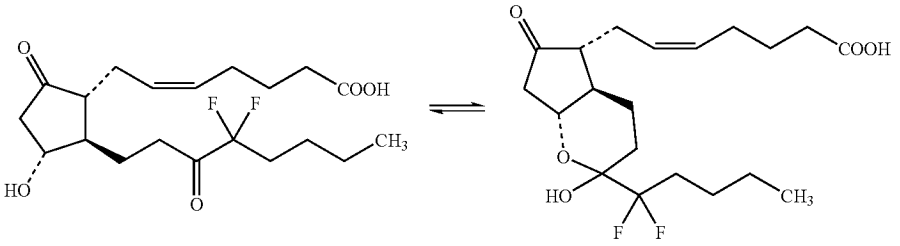
[35] [36]

R = H or F

The preparations in the present invention are not construed to be limited to them, and suitable means for protection, oxidation, reduction and the like may be employed.

In the bi-cyclic-16-halogen compounds used in the present invention, enteropooling activity is remarkably enhanced when substituted by two halogen atoms, especially fluorine atoms, at the C-16 position independently of the structure and substituents of the five-membered ring or the existence of the double bonds or other substituents. Particularly preferable bi-cyclic-16-halogen compounds are those tautomers formed from mono-cyclic compounds having a ketone at the C-9 position and a hydroxyl group at the C-11 position in the five membered ring. Another preferable group is a bi-cyclic-16-halogen compound containing a 5,6-single bond, 5,6-double bond or those having the carbon number 20-22 where R_1 contains 4 to 6 carbon atoms preferably in a straight chain.

An example of a mono-cyclic/bi-cyclic-16-halogen compound containing a 5,6-double bond are set forth below:



Another embodiment of the present invention comprises the composition of the present invention and a medium chain fatty acid triglyceride. The triglyceride may be a saturated or unsaturated fatty acid having 6-14 carbon atoms that may have a branched chain. A preferred fatty acid is a straight chain saturated fatty acid, for example, caproic acid, caprylic acid, capric acid, lauric acid and myristic acid. 2 or more medium chain fatty acid triglycerides may be used as a mixture.

The composition of the present invention may be dissolved or admixed in the medium chain fatty acid triglyceride. The amount of the medium chain fatty acid triglyceride is not limited. However, generally, 1-1,000,000 parts by weight of the medium chain fatty acid triglyceride based on one part by weight of the bi-cyclic structure may be used. Preferably, 5-500,000 parts by weight, and more preferably 10-200,000 parts by weight.

Examples of the medium chain fatty acid triglyceride used in the present invention include a triglyceride of a saturated or unsaturated fatty acid having 6-14 carbon atoms which may have a branched chain. Preferred fatty acid is a straight chain saturated fatty acid for example caproic acid (C6), caprylic acid (C8), capric acid (C10), lauric acid (C12) and myristic acid (C14). In addition, 2 or more medium chain fatty acid triglycerides may be used.

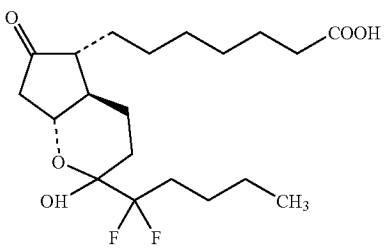
Even more non-polar solvents, such as commercially available Miglyol can be employed to increase the bi-cyclic/mono-cyclic ratio.

To exemplify formulation of an embodiment of the present invention and to illustrate potential effect of steric hinderance, an Example is set forth.

EXAMPLE

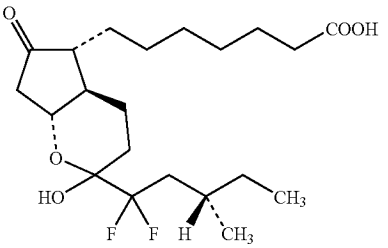
The following compounds 1 and 2 were dissolved in a medium chain fatty acid triglyceride (MCT=mixture of caprylic acid triglyceride and capric acid triglyceride in a ratio of 85:15) in an amount shown in the table below.

compound 1



-continued

compound 2



Each of the solutions was placed in a container made of hard glass and stored at 40° C. The time-course content of compound 1 and 2 in the solutions were determined by HPLC method. At the same time, each of compounds 1 and 2 was placed solely (without being dissolved in the solvent) in the container as above, and stored at 40° C. to provide control study.

(1) In the absence of the solvent, the content of the compounds was determined as follows by the HPLC method.

Stored compounds 1 and 2, and standard compounds 1 and 2 were weighed precisely around 0.025 g each, and exactly 5 mL aliquots of internal standard solution were added to the respectively weighed compounds. Test and standard preparations were obtained by adding acetonitrile (liquid chromatograph grade) to give the precise total amount of 10 mL each. Each 10 μL of the test and standard preparations were loaded on liquid chromatograph and determined the content of the compound by internal standard method with one point calibration curve.

$$\text{content (\%)} = \frac{Q_T}{Q_S} \times W_S \times \frac{100}{W_T}$$

W_X: The amount of the compound in the standard preparation (mg)

W_T: The amount of compound 1 and 2 in the test preparation.

Q_S: Peak area ratio of the compound in the standard preparation to the internal standard.

Q_T: Peak area ratio of the compound in the test preparation to the internal standard.

Measurement Conditions:

Detector: Ultraviolet absorption spectrophotometer (wavelength 294 nm)

Column: A stainless tube having about 5 mm of internal diameter and about 25 cm of length, packed with 5 μm octadecylsilyl silica gel for liquid chromatograph

Column temperature: Stable around 35° C.

Mobile phase: Mixed solution of acetonitrile (liquid chromatograph grade)/aqueous sodium acetate (0.01 mol/L)/glacial acetic acid (800:200:1)

(2) In the presence of the solvent, the content of the compound was determined as follows by HPLC method.

Based on the value expressed in the above table, an amount of the solution corresponding to 36 μg of compounds 1 and 2 was weighed precisely. Precisely 1.0 mL of an internal standard solution was added, and then ethyl acetate, (liquid chromatograph grade) was added to give a total amount of 10 mL each. Each 0.1 mL of the solution was vacuum concentrated to dryness to give the test preparation.

Each 18 mg of the standard compounds was weighed precisely and admixed with ethyl acetate (liquid chromatograph grade) to give the total amount of exactly 50 mL each. 1.0 mL of the solution and 10.0 mL of the internal standard solution were measured precisely and admixed with ethyl acetate (liquid chromatograph grade) to give a total of 100 mL each. Each 0.1 mL of the solution was vacuum concentrated to dryness to give the standard preparation.

To the test and standard preparations, 0.1 mL of fluorescent labeling reagent and 0.85 mL of fluorescent labeling catalyst were added, respectively, and the mixture was stirred and reacted at room temperature for more than 30 minutes. 0.05 mL aliquots of acetonitrile (liquid chromatograph grade) containing 2% acetic acid were added to the reaction mixtures, respectively, stirred, and then allowed to stand for more than 30 minutes to provide test and standard solutions.

Each 10 μL of the test and standard solution was loaded on liquid chromatograph and determined the content of the respective compounds by internal standard method with one point calibration curve.

$$\text{content } (\%) = \frac{Q_T}{Q_S} \times W_S \times \frac{100}{18}$$

W_X: The amount of the compound in the standard preparation (mg)

Q_S: Peak area ratio of the compound in the standard preparation to the internal standard.

Q_T: Peak area ratio of the compound in the test preparation to the internal standard.

Measurement Conditions:

Detector: Fluorescent spectrometer (excitation wavelength 259 nm; fluorescent wavelength 394 nm)

Column: A stainless tube having about 5 mm of internal diameter and about 25 cm of length, packed with 5 μm octadecylsilyl silica gel for liquid chromatograph

Column temperature: Stable at around 35° C.

Mobile phase: Mixed solution of acetonitrile (liquid chromatograph grade)/methanol (liquid chromatograph grade)/aqueous ammonium acetate (0.05 mol/L) (4:11:5)

The composition of the present invention causes extremely great enteropooling effect, inhibiting absorption of water in intestines. Further, the present compounds have no or greatly reduced, if any, intestinal contraction effect which PGEs or PGFs may possess. Therefore, the present composition treats constipation without malaise in belly owing to the intestinal contraction, such as bellyache. In addition, the present compound allows constipation to subside effecting normal bowl conditions. Moreover, it requires little time to recover from diarrhea symptoms if caused by the present compounds which possess great promotion effect of intraintestinal transportation. Therefore, they are even very useful as cathartics.

The composition of the present invention can be used as constipation treatment and prevention remedies for animals and humans, and, in general, used for systemic or local applications by oral administration, or as suppository, enema and the like. Sometimes, they may be applied as intravenous or subcutaneous injection. The dosage varies depending on animals, humans, age, weight, conditions, therapeutic effect, administration route, treatment time and the like. Preferably, it is 0.001-1,000 μg/kg, and more preferably 0.01 to 100 μg/kg.

The solid composition for oral administration of the present invention includes tablets, preparations, granules and the like. In such a solid composition, one or more active ingredients may be mixed with at least one inactive diluent, for example, lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinyl pyrrolidone, magnesium aluminate metasilicate and the like. According to the usual work-up, the composition may contain additives other than inactive diluent, for example, lubricant such as magnesium stearate; disintegrant such as fibrous calcium gluconate; stabilizer such as cyclodextrin, for example, α,β- or γ-cyclodextrin; etherified cyclodextrin such as dimethyl-α-, dimethyl-β-, trimethyl-β- or hydroxypropyl-β-cyclodextrin; branched cyclodextrin such as glucosyl-, maltosyl-cyclodextrin; formylated cyclodextrin, cyclodextrin containing sulfur; phospholipid and the like. When the above cyclodextrins are used, inclusion compound with cydodextrins may be sometimes formed to enhance stability. Alternatively, phospolipid may be sometimes used to form liposome, resulting in enhanced stability.

Tablets or pills may be coated with film soluble in the stomach or intestine such as sugar, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose phthalate as needed. Further, they may be formed as capsules with absorbable substances such as gelatin.

A liquid composition for oral administration may contain pharmaceutically acceptable emulsion, solution, suspension, syrup, elixi as well as generally used inactive diluent. Such composition may contain, in addition to the inactive diluent, adjuvants such as suspensioning agents, sweetening agents, flavoring agents, preservatives, solubilizers, anti-oxidants and the like. The details of the additives may be selected from those described in any general textbooks in the pharmaceutical field. Such liquid compositions may be directly enclosed in soft capsules. However, the selection of a diluent other than those mentioned above, which the bi-cyclic/mono-cyclic compound may be dissolved or admixed in, must carefully be selected so as not to affect the bi-cyclic/mono-cyclic ratio.

		initial	6 days	7 days	14 days	28 days	38 days	90 days	191 days
compound 1	crystal	100		97.2	94.1	87.4			
	MCT[1]	100			101.4		102.1	100.9	
compound 2	crystal	100	84.5		75.0	53.4			
	MCT[2]	100			99.6	98.9			99.6

[1]compound 1/solvent: 0.36 mg/g

[2]compound 2/solvent: 0.12 mg/g

Solutions for parenteral administration, for example, suppository, enema and the like according to the present invention include steril, aqueous or non-aqueous solution, suspension, emulsion and the like. The aqueous solution and suspension includes, for example, distilled water, physiological saline and Ringer's solution.

The non-aqueous solution and suspension include, for example, propylene glycol, polyethylene glycol, fatty acid triglyceride, vegetable oil such as olive oil, alcohols such as ethanol, polysorbate and the like. Such composition may contain adjuvants such as preservatives, wetting agent, emulsifier, dispersant, anti-oxidants and the like.

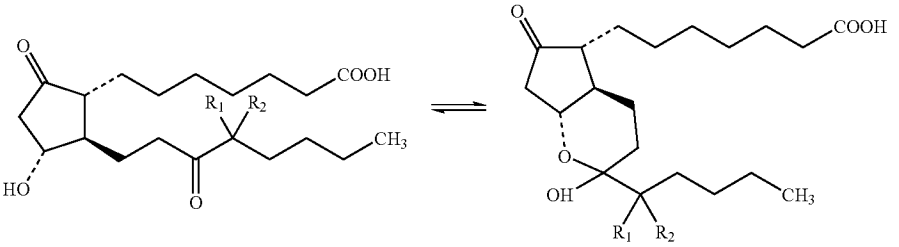
The present invention will be illustrated in the following examples. Which are illustrated by way of example only and not intended to limit the scope of the present invention.

Correlation of Mono-Cyclic/Bi-Cyclic Structure and Biological Activity

To exemplify the effect of halogenated-bi-cyclic compounds with halogen atoms at the C-16 position in the composition of the present invention, the following Examples were prepared and tested.

Example 1

The biological activity of compositions due to the ratios of mono-cyclic/bi-cyclic structures when Z of general formula (I) is an oxygen atom, and a ketone is present at the C-9 position of the present invention can be seen from the following examples. The number of fluorine atoms at the C-16 position and the ratio of mono-cyclic/bi-cyclic structures are shown in Table 1.



Enteropooling tests and diarrhea tests were conducted. The results are set forth in Table 1. The dose that raise the intraintestinal content by 50% was referred to as ED_{50}.

TABLE 1

	Example A	Example B	Comparative Example A
Number of F atoms at C-16 position	2	1	0
Ratio of mono-cyclic/bi-cyclic structure*	4:96	1:1	No signal derived from bi-cyclic structure was detected.
Enteropooling activity, ED_{50}	0.6 μg/kg	2 μg/kg	320 μg/kg
Diarrhea in mice	+: at 3 mg/kg (PO[1]) +: at 0.3 mg/kg (SC[2])	±: at 0.3 mg/kg (SC)	−: at 10 mg/kg (PO) −: at 1 mg/kg (SC)

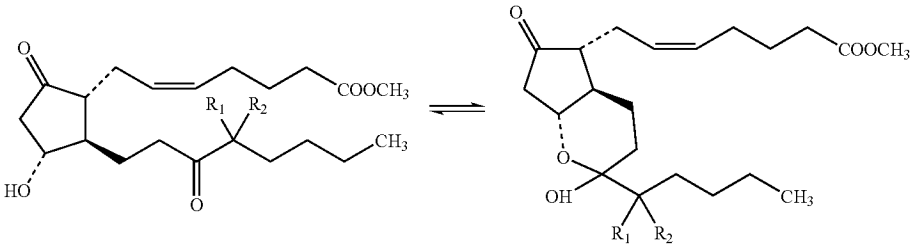
*Determined by NMR measurement in $CDCl_3$ solution.

[1]PO is by mouth (oral administration)

[2]SC is subcutaneous administration

Example 2

The biological activity of the composition due to the ratios of mono-cyclic/bi-cyclic structures when Z in Formula (I) is an oxygen, a ketone is present at the C-9 position, and there is a double bond between the 5,6-carbons is shown below.



Enteropooling tests and diarrhea tests were conducted. The results are set forth below in Table 2. The dose that raise the intraintestinal content by 50% was referred to as ED_{50}.

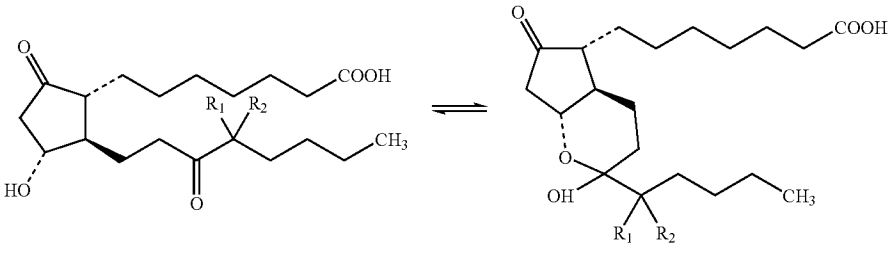
TABLE 2

	Example C	Example D	Comparative Example C
Number of F atoms at C-16 position	2	1	0
Ratio of mono-cyclic/bi-cyclic structure*	4:96	1:1	no signal derived from bi-cyclic structure was detected.
Enteropooling activity, ED_{50}	0.3 μg/kg	3 μg/kg	220 μg/kg
Diarrhea in mice	+: at 1 mg/kg (PO)[1]	−: at 1 mg/kg (PO) +: at 5 mg/kg (PO)	−: at 10 mg/kg (PO)

*Determined by NMR measurement in $CDCl_3$ solution.
[1]PO is by mouth (oral administration)

Effect of the Present Invention Dissolved in Medium Chain Fatty Acid Triglyceride on Bowel Movement After Single Oral Administration to Healthy Male Volunteers

3 to 9 healthy male volunteers were treated with a composition containing the following mono-cyclic/bi-cyclic structures (in $CDCl_3$) in a ratio of 4:96.



The test substance (R_1 and R_2 are F atoms) was dissolved in Panacet 800 (medium chain fatty acid triglyceride manufactured by Nippon Oil & Fat co., Ltd., Amagasaki, Japan) and filled in a capsule (each capsule contains 200 L of the mixture). Each subject was administered one capsule with 100 mL of water.

Table 3 shows the number of subjects who experienced loose stool or diarrhea.

TABLE 3

	Number of Subjects	
Dose	Normal	Loose or Diarrhea
5 μg	1/3	2/3
10 μg	5/7	2/7

TABLE 3-continued

	Number of Subjects	
Dose	Normal	Loose or Diarrhea
20 μg	1/3	2/3
30 μg	2/9	7/9

While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

What is claimed is:

1. A method for relieving constipation in a constipated patient or cleansing the bowel of a patient, comprising administering to said patient a therapeutically effective amount of a composition comprising the bi-cyclic and mono-cyclic tautomers of 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E1, wherein the ratio of the bi-cyclic to mono-cyclic tautomer is at least 1:1.

2. The method according to claim **1**, wherein the ratio of bi-cyclic to mono-cyclic tautomer is at least 20:1.

3. The method according to claim **1**, wherein the ratio of bi-cyclic to mono-cyclic tautomer is about 96:4.

4. A method for relieving constipation in a constipated patient or cleansing the bowel of a patient, comprising administering to said patient a therapeutically effective amount of a composition comprising the bi-cyclic and mono-cyclic tautomers of 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E1,and at least one medium fatty acid triglyceride, wherein the ratio of the bi-cyclic to mono-cyclic tautomer is at least 1:1.

5. The method according to claim **4**, wherein said medium chain fatty acid triglyceride is a triglyceride of fatty acid having 6-14 carbon atoms.

6. The method according to claim **4**, wherein the triglyceride is present in an amount of 1-1,000,000 parts by weight based on one part by weight of the bi-cyclic structure.

7. The method according to claim **4**, wherein the triglyceride is present in an amount of 5-500,000 parts by weight based on one part by weight of the bi-cyclic structure.

8. The method according to claim **4**, wherein the triglyceride is present in an amount of 10-200,000 parts by weight based on one part by weight of the bi-cyclic structure.

9. The method according to claim **4**, wherein said triglyceride is caprylic acid triglyceride and/or capric acid triglyceride.

10. The method according to claim **4**, wherein the ratio of bi-cyclic to mono-cyclic tautomer is at least 20:1.

11. The method according to claim **4**, wherein the ratio of bi-cyclic to mono-cyclic tautomer is about 96:4.

12. The method according to claim **1**, wherein the composition is free of water.

13. The method according to claim **4**, wherein the composition is free of water.

14. A method for treating constipation in a constipated patient or cleansing the bowel of a patient, comprising administering to said patient a therapeutically effective amount of a composition comprising the bi-cyclic and mono-cyclic tautomers of 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E1, wherein the ratio of the bi-cyclic to mono-cyclic tautomer is at least 1:1.

15. The method according to claim **14**, wherein the ratio of bi-cyclic to mono-cyclic tautomer is at least 20:1.

16. The method according to claim **14**, wherein the ratio of bi-cyclic to mono-cyclic tautomer is about 96:4.

17. The method according to claim **14**, wherein the tautomers are present in the absence of water in the composition.

18. A method for treating constipation in a constipated patient or cleansing the bowel of a patient, comprising administering to said patient a therapeutically effective amount of a composition comprising the bi-cyclic and mono-cyclic tautomers of 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E1, and at least one medium fatty acid triglyceride, wherein the ratio of the bi-cyclic to mono-cyclic tautomer is at least 1:1.

19. The method according to claim **18**, wherein said medium chain fatty acid triglyceride is a triglyceride of a fatty acid having 6-14 carbon atoms.

20. The method according to claim **18**, wherein the triglyceride is present in an amount of 1-1,000,000 parts by weight based on one part by weight of the bi-cyclic structure.

21. The method according to claim **18**, wherein the triglyceride is present in an amount of 5-500,000 parts by weight based on one part by weight of the bi-cyclic structure.

22. The method according to claim **18**, wherein the triglyceride is present in an amount of 10-200,000 parts by weight based on one part by weight of the bi-cyclic structure.

23. The method according to claim **18**, wherein said triglyceride is caprylic acid triglyceride and/or capric acid triglyceride.

24. The method according to claim **18**, wherein the ration of bi-cyclic to mono-cyclic tautomer is at least 20:1.

25. The method according to claim **18**, wherein the ratio of bi-cyclic to mono-cyclic tautomer is about 96:4.

26. The method according to claim **18**, wherein the tautomers are present in the absence of water in the composition.

* * * * *

Exhibit C

US007795312B2

(12) **United States Patent**
Ueno et al.

(10) **Patent No.: US 7,795,312 B2**
(45) **Date of Patent: Sep. 14, 2010**

(54) **METHOD FOR TREATING ABDOMINAL DISCOMFORT**

(75) Inventors: **Ryuji Ueno**, Montgomery, MD (US); **Sachiko Kuno**, Montgomery, MD (US)

(73) Assignee: **Sucampo AG**, Zug (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 263 days.

(21) Appl. No.: **10/745,689**

(22) Filed: **Dec. 29, 2003**

(65) **Prior Publication Data**

US 2004/0138308 A1 Jul. 15, 2004

Related U.S. Application Data

(60) Provisional application No. 60/436,462, filed on Dec. 27, 2002, provisional application No. 60/436,463, filed on Dec. 27, 2002.

(51) **Int. Cl.**
A61K 31/5575 (2006.01)

(52) **U.S. Cl.** **514/573**

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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Primary Examiner—Phyllis G. Spivack
(74) *Attorney, Agent, or Firm*—Sughrue Mion, PLLC

(57) **ABSTRACT**

A method for treating irritable bowel syndrome in a mammalian subject includes administering an effective amount of 13,14-dihydro-15-keto-16,16-difluoro-18-methyl-prostaglandin E_1 or 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E_1, or a salt, ether, ester or amide thereof, to the subject. A method for treating abdominal discomfort associated with irritable bowel syndrome in a mammalian subject includes administering an effective amount of 13,14-dihydro-15-keto-16,16-difluoro-18-methyl-prostaglandin E_1 or 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E_1, or a salt, ether, ester or amide thereof, to the subject.

22 Claims, No Drawings

METHOD FOR TREATING ABDOMINAL DISCOMFORT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of provisional application Nos. 60/436,462 and 60/436,463 both filed Dec. 27, 2002, the contents of which are incorporated herein by reference in their entireties.

TECHNICAL FIELD

The present invention relates to a method for treating abdominal discomfort with a chloride channel opener, especially, a prostaglandin compound.

Further, the present invention relates to a method for treating functional gastrointestinal disorders with a chloride channel opener, especially, a prostaglandin compound.

BACKGROUND ART

Abdominal indefinite complaint or abdominal discomfort is most often experienced in our daily lives, and it includes heartburn, nausea, emesis, anorexia, epigastric pain, abdominal bloating, chronic abdominal pain, abdominal discomfort, abnormal bowel movement such as constipation and diarrhea and the like. Various disorders may cause abdominal discomfort. It is also known that abdominal discomfort may also occur as a side effect of drug, medication or surgical procedure. However, it is not yet known as to the drug that may be used for safely and effectively treating abdominal discomfort.

Patients having functional gastrointestinal disorders often report abdominal discomfort. Functional gastrointestinal disorders are characterized by chronic or recurrent gastrointestinal symptoms which are not explained by any organic, i.e. structural or biochemical, abnormality. In general, functional disorders should be distinguished from morphological or organic disorders in which the organ structures have been abnormally changed. An organic disorder may accompany functional abnormality of organs but it is surely possible to diagnose if there is any underlying organic abnormality.

Stress may effect on various organs in various ways, and the typical example of such organs is gastrointestinal tract. The interaction among stress-brain-gastrointestinal organ is called brain-gut axis, and now a days, it draws great interest of the art. In the field of clinical medicine, a group of functional disorders in which the brain-gut axis plays a central role of the pathology is called functional gastrointestinal disorders.

Typical examples of functional gastrointestinal disorders include irritable bowel syndrome (IBS) and functional dyspepsia (FD). These terms are not used for exclusively determining the nature of separate disorders but most commonly used for expressing various overlapping symptoms manifested in the upper and lower gastrointestinal tracts.

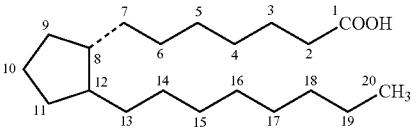
IBS is an archetype disorder of functional gastrointestinal disorders with no underlying organic abnormality. IBS patient reports continued lower gastrointestinal symptoms such as abnormal bowel movement, abdominal pain, abdominal bloating and abdominal discomfort, as well as upper gastrointestinal symptoms such as epigastric pain, hypochondriac pain, nausea, anorexia, borborygmus, vomiting, belching and heartburn.

FD patient has no underlying organic disorder such as ulcer and reports continued upper gastrointestinal tract symptoms such as abdominal pain, nausea, anorexia and slow digestion. The term "dyspepsia" means chronic or repetitious pain or discomfort mainly occurring in epigastric region. Up to 60% of the dyspepsia patients have no underlying organic disorder and are diagnosed as FD.

As explained above, functional gastrointestinal disorders are a group of disorders in which the gastrointestinal symptoms continue for a long period or by repeating a period of recrudescence and palliation without clear organic abnormalities. No systematic method has been established for treating such disorder.

Prostaglandins (hereinafter, referred to as PG(s)) are members of class of organic carboxylic acids, which are contained in tissues or organs of human or other mammals, and exhibit a wide range of physiological activity. PGs found in nature (primary PGs) generally have a prostanoic acid skeleton as shown in the formula (A):

(A)



On the other hand, some of synthetic analogues of primary PGs have modified skeletons. The primary PGs are classified to PGAs, PGBs, PGCs, PGDs, PGEs, PGFs, PGGs, PGHs, PGIs and PGJs according to the structure of the five-membered ring moiety, and further classified into the following three types by the number and position of the unsaturated bond at the carbon chain moiety:

Subscript 1: 13,14-unsaturated-15-OH

Subscript 2: 5,6- and 13,14-diunsaturated-15-OH

Subscript 3: 5,6-, 13,14-, and 17,18-triunsaturated-15-OH.

Further, the PGFs are classified, according to the configuration of the hydroxyl group at the 9-position, into α type (the hydroxyl group is an α-configuration) and β type (the hydroxyl group is a β-configuration).

PGE_1 and PGE_2 and PGE_3 are known to have vasodilation, hypotension, gastric secretion decreasing, intestinal tract movement enhancement, uterine contraction, diuretic, bronchodilation and anti ulcer activities. $PGF_{1\alpha}$, $PGF_{2\alpha}$ and $PGF_{3\alpha}$ have been known to have hypertension, vasoconstriction, intestinal tract movement enhancement, uterine contraction, lutein body atrophy and bronchoconstriction activities.

The present inventor already found that prostaglandin compounds open chloride channels, especially ClC channels, more especially ClC-2 channel (WO 03/030912, this reference is herein incorporated by reference).

However, it is not known how chloride channel openers and/or prostaglandin compounds act on abdominal discomfort, or the functional gastrointestinal disorders.

DISCLOSURE OF THE INVENTION

The present inventor has conducted intensive studies and found that a chloride channel opener, especially prostaglandin compound have a significant effect on abdominal discomfort, especially, on functional gastrointestinal disorders such as IBS and FD, which resulted in the completion of the present invention.

Namely, the present invention relates to a method for treating abdominal discomfort in a mammalian subject, which

comprises administration of an effective amount of a chloride channel opener, especially ClC channel opener, more especially ClC-2 opener such as prostaglandin compound to the subject.

The present invention further relates to a pharmaceutical composition for treating abdominal discomfort in a mammalian subject, which comprises an effective amount of a chloride channel opener, especially ClC channel opener, more especially ClC-2 channel opener such as prostaglandin compound.

Further more, the present invention relates to a use of a chloride channel opener, especially ClC channel opener, more especially ClC-2 channel opener such as prostaglandin compound for manufacturing a pharmaceutical composition for treating abdominal discomfort in a mammalian subject.

Another embodiment of the present invention relates to a method for treating functional gastrointestinal disorders in a mammalian subject, which comprises administration of an effective amount of a chloride channel opener, especially ClC channel opener, more especially ClC-2 channel opener such as prostaglandin compound to the subject.

The present invention further relates to a pharmaceutical composition for treating functional gastrointestinal disorders in a mammalian subject, which comprises an effective amount of a chloride channel opener, especially ClC channel opener, more especially ClC-2 channel opener such as prostaglandin compound.

Further more, the present invention relates to a use of a chloride channel opener, especially ClC channel operator, more especially ClC-2 channel such as prostaglandin compound for manufacturing a pharmaceutical composition for treating functional gastrointestinal disorders in a mammalian subject.

DETAILED DESCRIPTION OF THE INVENTION

The chloride channel opener used in the present invention is not particularly limited and may be any compound as far as it has a chloride channel opening activity. The chloride channel opening activity may be confirmed by measuring the increase of chloride-ion flows through a chloride channel in a cell membrane from inside to outside of the cell or in the opposite direction. For instance, it is possible to carry out a screening for a compound having chloride channel opening activity by using a known assay strategy such as the patch clamp. Preferred chloride channel opener is a ClC channel opener, especially a ClC-2 channel opener.

Examples of compounds having the opening activity of a ClC-2 channel include cyclooxygenase inhibitor, nonsteroidal anti-inflammatory agent (e.g. ibuprofen and ebselen), protein kinase A, oleic acid, elaidic acid, arachiodonic acid, cell growth factor (e.g., TGFα (transforming growth factor-α) and KGF (keratinocyte growth factor)), benzimidazole derivative and prostaglandin compound. Preferred compound of the present invention is a prostaglandin compound.

The nomenclature of the prostaglandin compounds used herein is based on the numbering system of the prostanoic acid represented in the above formula (A).

The formula (A) shows a basic skeleton of the C-20 carbon atoms, but the present invention is not limited to those having the same number of carbon atoms. In the formula (A), the numbering of the carbon atoms which constitute the basic skeleton of the PG compounds starts at the carboxylic acid (numbered 1), and carbon atoms in the α-chain are numbered 2 to 7 towards the five-membered ring, those in the ring are 8 to 12, and those in the ω-chain are 13 to 20. When the number of carbon atoms is decreased in the α-chain, the number is deleted in the order starting from position 2; and when the number of carbon atoms is increased in the α-chain, compounds are named as substitution compounds having respective substituents at position 2 in place of the carboxy group (C-1). Similarly, when the number of carbon atoms is decreased in the ω-chain, the number is deleted in the order starting from position 20; and when the number of carbon atoms is increased in the ω-chain, the carbon atoms beyond position 20 are named as substituents. Stereochemistry of the compounds is the same as that of the above formula (A) unless otherwise specified.

In general, each of the terms PGD, PGE and PGF represents a PG compound having hydroxy groups at positions 9 and/or 11, but in the present specification, these terms also include those having substituents other than the hydroxy group at positions 9 and/or 11. Such compounds are referred to as 9-dehydroxy-9-substituted-PG compounds or 11-dehydroxy-11-substituted-PG compounds. A PG compound having hydrogen in place of the hydroxy group is simply names as 9- or 11-dehydroxy-PG compound.

As stated above, the nomenclature of the PG compounds is based on the prostanoic acid skeleton. However, in case the compound has a similar partial structure as a prostaglandin, the abbreviation of "PG" may be used. Thus, a PG compound of which α-chain is extended by two carbon atoms, that is, having 9 carbon atoms in the α-chain is named as 2-decarboxy-2-(2-carboxyethyl)-PG compound. Similarly, a PG compound having 11 carbon atoms in the α-chain is named as 2-decarboxy-2-(4-carboxybutyl)-PG compound. Further, a PG compound of which ω-chain is extended by two carbon atoms, that is, having 10 carbon atoms in the ω-chain is named as 20-ethyl-PG compound. These compounds, however, may also be named according to the IUPAC nomenclatures.

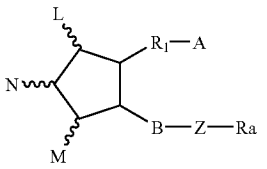
Examples of the analogs (including substituted derivative) or derivatives include a PG compound of which carboxy group at the end of α-chain is esterified; a compound of which α-chain is extended; physiologically acceptable salt thereof; a compound having a double bond at 2-3 position or a triple bond at position 5-6, a compound having substituent(s) at position 3, 5, 6, 16, 17, 18, 19 and/or 20; and a compound having lower alkyl or a hydroxy (lower) alkyl group at position 9 and/or 11 in place of the hydroxy group.

According to the present invention, preferred substituents at position 3, 17, 18 and/or 19 include alkyl having 1-4 carbon atoms, especially methyl and ethyl. Preferred substituents at position 16 include lower alkyl such as methyl and ethyl, hydroxy, halogen atoms such as chlorine and fluorine, and aryloxy such as trifluoromethylphenoxy. Preferred substituents at position 17 include lower alkyl such as methyl and ethyl, hydroxy, halogen atoms such as chlorine and fluorine, aryloxy such as trifluoromethylphenoxy. Preferred substituents at position 20 include saturated or unsaturated lower alkyl such as C1-4 alkyl, lower alkoxy such as C1-4 alkoxy, and lower alkoxy alkyl such as C1-4 alkoxy-C1-4 alkyl. Preferred substituents at position 5 include halogen atoms such as chlorine and fluorine. Preferred substituents at position 6 include an oxo group forming a carbonyl group. Stereochemistry of PGs having hydroxy, lower alkyl or hydroxy(lower) alkyl substituent at position 9 and/or 11 may be α, β or a mixture thereof.

Further, the above analogs or derivatives may be compounds having an alkoxy, cycloalkyl, cycloalkyloxy, phenoxy or phenyl group at the end of the ω-chain where the chain is shorter than the primary PGs.

A preferred compounds used in the present invention is represented by the formula (I):

(I)

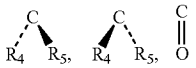


wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is —CH_3, or —CH_2OH, —$COCH_2OH$, —COOH or a functional derivative thereof;

B is single bond, —CH_2—CH_2—, —CH═CH—, —C≡C—, —CH_2—CH_2—CH_2—, —CH═CH—CH_2—, —CH_2—CH═CH—, —C≡C—CH_2— or —CH_2—C≡C—;

Z is



or single bond

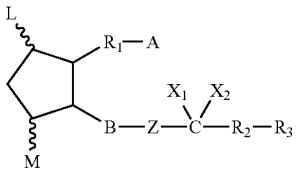
wherein R_4 and R_5 are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R_4 and R_5 are not hydroxy and lower alkoxy at the same time;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

Ra is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or hetrocyclic-oxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower) alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclic-oxy group.

A preferred compound used in the present invention is represented by the formula (II):

(II)

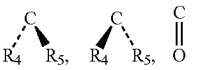


wherein L and M are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have one or more double bonds;

A is —CH_3, or —CH_2OH, —$COCH_2OH$, —COOH or a functional derivative thereof;

B is a single bond, —CH_2—CH_2—, —CH═CH—, —C≡C—, —CH_2—CH_2— CH_2—, —CH═CH—CH_2—, —CH_2—CH═CH—, —C≡C—CH_2— or —CH_2—C≡C—;

Z is



or single bond

wherein R_4 and R_5 are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R_4 and R_5 are not hydroxy and lower alkoxy at the same time;

X_1 and X_2 are hydrogen, lower alkyl, or halogen;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur;

R_2 is a single bond or lower alkylene; and

R_3 is lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclic-oxy group.

In the above formula, the term "unsaturated" in the definitions for R_1 and Ra is intended to include at least one or more double bonds and/or triple bonds that are isolatedly, separately or serially present between carbon atoms of the main and/or side chains. According to the usual nomenclature, an unsaturated bond between two serial positions is represented by denoting the lower number of the two positions, and an unsaturated bond between two distal positions is represented by denoting both of the positions.

The term "lower or medium aliphatic hydrocarbon" refers to a straight or branched chain hydrocarbon group having 1 to 14 carbon atoms (for a side chain, 1 to 3 carbon atoms are preferable) and preferably 1 to 10, especially 1 to 8 carbon atoms.

The term "halogen atom" covers fluorine, chlorine, bromine and iodine.

The term "lower" throughout the specification is intended to include a group having 1 to 6 carbon atoms unless otherwise specified.

The term "lower alkyl" refers to a straight or branched chain saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl.

The term "lower alkylene" refers to a straight or branched chain bivalent saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methylene, ethylene, propylene, isopropylene, butylene, isobutylene, t-butylene, pentylene and hexylene. The term "lower alkoxy" refers to a group of lower alkyl-O—, wherein lower alkyl is as defined above.

The term "hydroxy(lower)alkyl" refers to a lower alkyl as defined above which is substituted with at least one hydroxy group such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 1-methyl-1-hydroxyethyl.

The term "lower alkanoyloxy" refers to a group represented by the formula RCO-O—, wherein RCO- is an acyl group formed by oxidation of a lower alkyl group as defined above, such as acetyl.

The term "cyclo(lower)alkyl" refers to a cyclic group formed by cyclization of a lower alkyl group as defined above

but contains three or more carbon atoms, and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cyclo(lower)alkyloxy" refers to the group of cyclo(lower)alkyl-O—, wherein cyclo(lower)alkyl is as defined above.

The term "aryl" may include unsubstituted or substituted aromatic hydrocarbon rings (preferably monocyclic groups), for example, phenyl, tolyl, xylyl. Examples of the substituents are halogen atom and halo(lower)alkyl, wherein halogen atom and lower alkyl are as defined above.

The term "aryloxy" refers to a group represented by the formula ArO-, wherein Ar is aryl as defined above. The term "heterocyclic group" may include mono- to tri-cyclic, preferably monocyclic hetercyclic group which is 5 to 14, preferably 5 to 10 membered ring having optionally substituted carbon atom and 1 to 4, preferably 1 to 3 of 1 or 2 type of hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom. Examples of the heterocyclic group include furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, 2-pyrrolinyl, pyrrolidinyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, piperidino, piperazinyl, morpholino, indolyl, benzothienyl, quinolyl, isoquinolyl, purinyl, quinazolinyl, carbazolyl, acridinyl, phenanthridinyl, benzimidazolyl, benzimidazolinyl, benzothiazolyl, phenothiazinyl. Examples of the substituent in this case include halogen, and halogen substituted lower alkyl group, wherein halogen atom and lower alkyl group are as described above.

The term "heterocyclic-oxy group" means a group represented by the formula HcO-, wherein Hc is a heterocyclic group as described above.

The term "functional derivative" of A includes salts (preferably pharmaceutically acceptable salts), ethers, esters and amides.

Suitable "pharmaceutically acceptable salts" include conventionally used non-toxic salts, for example a salt with an inorganic base such as an alkali metal salt (such as sodium salt and potassium salt), an alkaline earth metal salt (such as calcium salt and magnesium salt), an ammonium salt; or a salt with an organic base, for example, an amine salt (such as methylamine salt, dimethylamine salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, tris (hydroxymethylamino)ethane salt, monomethyl- monoethanolamine salt, procaine salt and caffeine salt), a basic amino acid salt (such as arginine salt and lysine salt), tetraalkyl ammonium salt and the like. These salts may be prepared by a conventional process, for example from the corresponding acid and base or by salt interchange.

Examples of the ethers include alkyl ethers, for example, lower alkyl ethers such as methyl ether, ethyl ether, propyl ether, isopropyl ether, butyl ether, isobutyl ether, t-butyl ether, pentyl ether and 1-cyclopropyl ethyl ether; and medium or higher alkyl ethers such as octyl ether, diethylhexyl ether, lauryl ether and cetyl ether; unsaturated ethers such as oleyl ether and linolenyl ether; lower alkenyl ethers such as vinyl ether, allyl ether; lower alkynyl ethers such as ethynyl ether and propynyl ether; hydroxy(lower)alkyl ethers such as hydroxyethyl ether and hydroxyisopropyl ether; lower alkoxy (lower)alkyl ethers such as methoxymethyl ether and 1-methoxyethyl ether; optionally substituted aryl ethers such as phenyl ether, tosyl ether, t-butylphenyl ether, salicyl ether, 3,4-di-methoxyphenyl ether and benzamidophenyl ether; and aryl(lower)alkyl ethers such as benzyl ether, trityl ether and benzhydryl ether.

Examples of the esters include aliphatic esters, for example, lower alkyl esters such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester and 1-cyclopropylethyl ester; lower alkenyl esters such as vinyl ester and allyl ester; lower alkynyl esters such as ethynyl ester and propynyl ester; hydroxy(lower) alkyl ester such as hydroxyethyl ester; lower alkoxy (lower) alkyl esters such as methoxymethyl ester and 1-methoxyethyl ester; and optionally substituted aryl esters such as, for example, phenyl ester, tolyl ester, t-butylphenyl ester, salicyl ester, 3,4-di-methoxyphenyl ester and benzamidophenyl ester; and aryl(lower)alkyl ester such as benzyl ester, trityl ester and benzhydryl ester.

The amide of A mean a group represented by the formula —CONR'R", wherein each of R' and R" is hydrogen, lower alkyl, aryl, alkyl- or aryl-sulfonyl, lower alkenyl and lower alkynyl, and include for example lower alkyl amides such as methylamide, ethylamide, dimethylamide and diethylamide; arylamides such as anilide and toluidide; and alkyl- or arylsulfonylamides such as methylsulfonylamide, ethylsulfonylamide and tolylsulfonylamide.

Preferred examples of L and M include hydroxy and oxo, and especially, M is hydroxy and L is oxo which as a 5-membered ring structure of, so called, PGE type. Preferred example of A is —COOH, its pharmaceutically acceptable salt, ester or amide thereof.

Preferred example of X_1 and X_2 is fluorine, so called 16,16-difluoro type.

Preferred R_1 is a hydrocarbon residue containing 1-10 carbon atoms, preferably 6-10 carbon atoms. Further, at least one carbon atom in the alipahtic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur. Examples of R_1 include, for example, the following groups:

—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH═CH—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH═CH—,
—CH_2—C≡C—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—O—CH_2—,
—CH_2—CH═CH—CH_2—O—CH_2—,
—CH_2—C≡C—CH_2—O—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH═CH—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—CH═CH—,
—CH_2—C≡C—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—CH(CH_3)—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH(CH_3)—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH═CH—CH_2—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH═CH—,
—CH_2—C≡C—CH_2—CH_2—CH_2—CH_2—CH_2—, and
—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH(CH_3)—CH_2—.

Preferred Ra is a hydrocarbon containing 1-10 carbon atoms, more preferably, 1-8 carbon atoms. Ra may have one or two side chains having one carbon atom.

The configuration of the ring and the α- and/or ω chains in the above formula (I) and (II) may be the same as or different from that of the primary PGs. However, the present invention also includes a mixture of a compound having a primary type configuration and a compound of a non-primary type configuration.

In the present invention, the PG compound which is dihydro between 13 and 14, and keto (═O) at 15 position may be in the keto-hemiacetal equilibrium by formation of a hemiacetal between hydroxy at position 11 and keto at position 15.

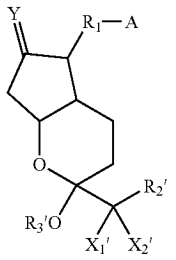
For example, it has been revealed that when both of X_1 and X_2 are halogen atoms, especially, fluorine atoms, the compound contains a tautomeric isomer, bicyclic compound.

If such tautomeric isomers as above are present, the proportion of both tautomeric isomers varies with the structure of the rest of the molecule or the kind of the substituent present. Sometimes one isomer may predominantly be present in comparison with the other. However, it is to be appreciated that the present invention includes both isomers.

Further, the 15-keto-PG compounds used in the invention include the bicyclic compound and analogs or derivative thereof.

The bicyclic compound is represented by the formula (III)

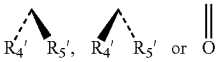
(III)



wherein, A is —CH_3, or —CH_2OH, —$COCH_2OH$, —COOH or a functional derivative thereof;

X_1' and X_2' are hydrogen, lower alkyl, or halogen;

Y is



wherein R_4' and R_5' are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R_4' and R_5' are not hydroxy and lower alkoxy at the same time.

R_1 is a saturated or unsaturated divalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

R_2' is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or hetrocyclic-oxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower) alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclic-oxy group.

R_3' is hydrogen, lower alkyl, cyclo(lower)alkyl, aryl or heterocyclic group.

Furthermore, while the compounds used in the invention may be represented by a formula or name based on keto-type regardless of the presence or absence of the isomers, it is to be noted that such structure or name does not intend to exclude the hemiacetal type compound.

In the present invention, any of isomers such as the individual tautomeric isomers, the mixture thereof, or optical isomers, the mixture thereof, a racemic mixture, and other steric isomers may be used in the same purpose.

Some of the compounds used in the present invention may be prepared by the method disclosed in U.S. Pat. Nos. 5,073,569, 5,166,174, 5,221,763, 5,212,324, 5,739,161 and 6,242,485 (these cited references are herein incorporated by reference).

The term "chloride or ClC or ClC-2 channel opener" used herein includes the compound which activates, promotes or modulates the Cl^- current, Cl^- secretion or Cl^- transport by opening chloride or ClC or ClC-2 channel.

According to the present invention a mammalian subject may be treated by the instant invention by administering the compound used in the present invention. The subject may be any mammalian subject including a human. The compound may be applied systemically or topically. Usually, the compound may be administered by oral administration, intravenous injection (including infusion), subcutaneous injection, intra rectal administration, intra vaginal administration, transdermal administration and the like. The dose may vary depending on the strain of the animal, age, body weight, symptom to be treated, desired therapeutic effect, administration route, term of treatment and the like. A satisfactory effect can be obtained by systemic administration 1-4 times per day or continuous administration at the amount of 0.001-1000 μg/kg per day, more preferably 0.01-100 μg/kg, most preferably 0.1-10 μg/kg.

A typical treatment regimen entails administering to a human patient a composition containing from about 18 to about 30 μg of active ingredient according to the invention from one to three times daily, with about 24 μg two times per day being preferred. The composition for the oral administration may be administered with or without food and/or water.

The compound may preferably be formulated in a pharmaceutical composition suitable for administration in a conventional manner. The composition may be those suitable for oral administration, injection or perfusion as well as it may be an external agent, suppository or pessary.

The composition of the present invention may further contain physiologically acceptable additives. Said additives may include the ingredients used with the present compounds such as excipient, diluent, filler, resolvent, lubricant, adjuvant, binder, disintegrator, coating agent, cupsulating agent, ointment base, suppository base, aerozoling agent, emulsifier, dispersing agent, suspending agent, thickener, tonicity agent, buffering agent, soothing agent, preservative, antioxidant, corrigent, flavor, colorant a functional material such as cyclodextrin and biodegradable polymer, stabilizer. The additives are well known to the art and may be selected from those described in general reference books of pharmaceutics.

The amount of the above-defined compound in the composition of the invention may vary depending on the formulation of the composition, and may generally be 0.00001-10.0 wt %, more preferably 0.0001-1.0 wt %, most preferably 0.001-0.1%.

Examples of solid compositions for oral administration include tablets, troches, sublingual tablets, capsules, pills, powders, granules and the like. The solid composition may be prepared by mixing one or more active ingredients with at least one inactive diluent. The composition may further contain additives other than the inactive diluents, for example, a lubricant, a disintegrator and a stabilizer. Tablets and pills may be coated with an enteric or gastroenteric film, if necessary. They may be covered with two or more layers. They may also be absorbed to a sustained release material, or microcapsulated. Additionally, the compositions may be capsulated by means of an easily degradable material such gelatin. They may be further dissolved in an appropriate solvent such as fatty acid or its mono, di or triglyceride to be a soft capsule. Sublingual tablet may be used in need of fast-acting property.

Examples of liquid compositions for oral administration include emulsions, solutions, suspensions, syrups and elixirs and the like. Said composition may further contain a conventionally used inactive diluents e.g. purified water or ethyl alcohol. The composition may contain additives other than the inactive diluents such as adjuvant e.g. wetting agents and suspending agents, sweeteners, flavors, fragrance and preservatives.

The composition of the present invention may be in the form of spraying composition, which contains one or more active ingredients and may be prepared according to a known method.

Examples of the injectable compositions of the present invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. Diluents for the aqueous solution or suspension may include, for example, distilled water for injection, physiological saline and Ringer's solution.

Non-aqueous diluents for solution and suspension may include, for example, propylene glycol, polyethylene glycol, vegetable oils such as olive oil, alcohols such as ethanol and polysorbate. The composition may further comprise additives such as preservatives, wetting agents, emulsifying agents, dispersing agents and the like. They may be sterilized by filtration through, e.g. a bacteria-retaining filter, compounding with a sterilizer, or by means of gas or radioisotope irradiation sterilization. The injectable composition may also be provided as a sterilized powder composition to be dissolved in a sterilized solvent for injection before use.

The present external agent includes all the external preparations used in the fields of dermatology and otolaryngology, which includes ointment, cream, lotion and spray.

Another form of the present invention is suppository or pessary, which may be prepared by mixing active ingredients into a conventional base such as cacao butter that softens at body temperature, and nonionic surfactants having suitable softening temperatures may be used to improve absorbability.

The term "treatment" used herein includes any means of control such as prevention, care, relief of the condition, attenuation of the condition and arrest of progression.

The term "abdominal discomfort" used herein includes any abdominal discomfort involved or being associated with any type of condition and/or diseases, or caused by drugs, medications or surgical procedures.

In the present specification and claims, "treatment of abdominal discomfort" or "treating abdominal discomfort" includes to relieve or to eliminate the abdominal discomfort. In addition, "treatment of functional gastrointestinal disorder" or "treating functional gastrointestinal disorder" covers to relieve or to eliminate abdominal discomfort which is associated with functional gastrointestinal disorders.

One of the typical disorders being accompanied by abdominal discomfort includes functional gastrointestinal disorders. Examples of the functional gastrointestinal disorders include irritable bowel syndrome and functional dyspepsia.

The pharmaceutical composition of the present invention may further contain other pharmacological ingredients as far as they do not contradict the purpose of the present invention.

The further details of the present invention will follow with reference to test examples, which, however, are not intended to limit the present invention.

EXAMPLE 1

Methods

Patients with irritable bowel syndrome (IBS) were randomly allocated to the following two treatment groups.

Group 1: Test substance (13,14-dihydro-15-keto-16,16-difluoro-PGE_1) 48 μg total (24 μg/breakfast+24 μg/dinner)

Group 2: Matching placebo (placebo/breakfast+placebo/dinner)

Each group underwent two weeks washout period and then began to administer oral test substance (capsules) or placebo (capsules) daily for 4 weeks. Test substance or placebo was taken two times a day (b.i.d) at breakfast with food and at least 8 ounces of water and at dinner with food and at least 8 ounces of water. Patients were asked to evaluate abdominal discomfort upon waking in the morning, using a 5-point scale (Score: 0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe) at 4 weeks after the initiation of the treatments.

Results

As shown in Table 1, test substance of this invention significantly improved the abdominal discomfort in the patients with IBS.

TABLE 1

Effect of test substance on abdominal discomfort in patients with IBS

	Abdominal discomfort score, Mean ± SD (N)	
Week	Placebo	Test Substance
Baseline	2.31 ± 0.788 (26)	2.25 ± 0.803 (32)
Week 4	2.19 ± 0.895 (26)	1.48 ± 1.029** (31)

Test substance: 13,14-dihydro-15-keto-16,16-difluoro-PGE_1

**$p < 0.01$ (van Elteren test stratified by center)

EXAMPLE 2

Method

Patients with occasional constipation were randomly allocated to the following two treatment groups.

Group 1: Test substance (13,14-dihydro-15-keto-16,16-difluoro-PGE1) 48 μg total (24 μg/breakfast+24 μg/dinner)

Group 2: Matching placebo (placebo/breakfast+placebo/dinner)

Each group underwent two weeks washout period and then began to administer oral test substance (capsules) or placebo (capsules) daily for 4 weeks. During the washout period, the patient's bowel habit was documented to confirm the existence of constipation. Constipation is defined as, on average, less than three spontaneous bowel movements per week. All existing laxative medication was withdrawn at the start of the washout period and the patients were instructed not to change their diet or lifestyle during the study.

Test substance or placebo was taken orally for a total treatment period of 4 weeks; it was taken two times a day (b.i.d) at

breakfast with food and at least 8 ounces of water and at dinner with food and at least 8 ounces of water.

The patients were asked to evaluate abdominal discomfort upon waking in the morning, using a 5-point scale (Score: 0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe) at 2 and 4 weeks after the initiation of the treatments.

Results

As shown in Table 2, test substance of this invention significantly improved the abdominal discomfort in patients with constipation.

TABLE 2

Effect of test substance on abdominal discomfort in patients with constipation

	Abdominal discomfort score, Mean ± SD (N)	
	Placebo	Test Substance
Week 2	1.41 ± 1.035 (122)	1.09 ± 1.047* (116)
Week 3	1.64 ± 1.114 (122)	1.27 ± 1.057* (117)
Week 4	1.52 ± 1.038 (122)	1.22 ± 1.060* (117)

Test substance: 13,14-dihydro-15-keto-16,16-difluoro-PGE_1
*$p < 0.05$ (van Elteren test stratified by center)

EXAMPLE 3

Methods

Patients with irritable bowel syndrome (IBS) were randomly allocated to the following two treatment groups.

Group 1: Test substance (13,14-dihydro-15-keto-16,16-difluoro-PGE_1) 48 μg total (24 μg/breakfast+24 μg/dinner)

Group 2: Matching placebo (placebo/breakfast+placebo/dinner)

Each group underwent two weeks washout period and then began to administer oral test substance (capsules) or placebo (capsules) daily for 4 weeks. Test substance or placebo was taken two times a day (b.i.d) at breakfast with food and at least 8 ounces of water and at dinner with food and at least 8 ounces of water. The patients were asked to evaluate abdominal bloating upon waking in the morning, using a 5-point scale (Score: 0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe) at 4 weeks after the initiation of the treatments.

Results

As shown in Table 3, test substance of this invention significantly improved the abdominal bloating in patients with IBS.

TABLE 3

Effect of test substance on abdominal bloating in patients with IBS

	Abdominal bloating score, Mean ± SD (N)	
Week	Placebo	Test Substance
Baseline	2.46 ± 0.859 (26)	2.50 ± 0.916 (32)
Week 4	2.42 ± 0.945 (26)	1.74 ± 0.999** (31)

Test substance: 13,14-dihydro-15-keto-16,16-difluoro-PGE_1
**$p < 0.01$ (van Elteren test stratified by center)

EXAMPLE 4

Methods

Patients with irritable bowel syndrome (IBS) exhibiting dyschezia were randomly allocated to the following two treatment groups.

Group 1: Test substance (13,14-dihydro-15-keto-16,16-difluoro-PGE_1) 48 μg total (24 μg/breakfast+24 μg/dinner)

Group 2: Matching placebo (placebo/breakfast+placebo/dinner)

Each group underwent two weeks washout period and then began to administer oral test substance (capsules) or placebo (capsules) daily for 4 weeks. Test substance or placebo was taken two times a day (b.i.d) at breakfast with food and at least 8 ounces of water and at dinner with food and at least 8 ounces of water. After 3 consecutive days of not having spontaneous bowel movement, the investigator could prescribe to the patient 10 mg bisacodyl suppository as a rescue medication. If this was not effective, Fleet® enema could be used. During the study period, each patient documented bowel activity. A spontaneous bowel movement was defined as any bowel movement except for that occurred within 24 hours after the rescue medication. Frequency of spontaneous bowel movements at Baseline, Weeks 1, 2, 3 and 4 were analyzed.

Results

As shown in Table 4, test substance of this invention significantly improved the spontaneous bowel movement frequency in patients with IBS exhibiting dyschezia.

TABLE 4

Effect of test substance on spontaneous bowel movement frequency rates in patients with IBS exhibiting dischezia

	Spontaneous Bowel Movement Frequency Rates, Mean ± SD (N)	
Week	Placebo	Test Substance
Baseline	1.85 ± 2.310 (26)	1.43 ± 0.773 (32)
Week 1	3.58 ± 2.887 (26)	6.50 ± 4.108** (32)
Week 2	2.84 ± 2.481 (26)	5.58 ± 4.003** (32)
Week 3	2.30 ± 2.170 (26)	5.93 ± 4.775** (32)
Week 4	2.21 ± 2.399 (26)	5.17 ± 4.333* (32)

Test substance: 13,14-dihydro-15-keto-16,16-difluoro-PGE_1
*$p < 0.05$, ** $p < 0.01$ (van Elteren test stratified by center)

What is claimed is:

1. A method for treating irritable bowel syndrome in a mammalian subject, which comprises administering an effective amount of 13,14-dihydro-15-keto-16,16-difluoro-18-methyl-prostaglandin E_1, or a salt, ether, ester or amide thereof, to the subject.

2. The method as described in claim **1**, which comprises administering an effective amount of 13,14-dihydro-15-keto-16,16-difluoro-18-methyl-prostaglandin E_1, or a pharmaceutically acceptable salt, ester or amide thereof.

3. The method as described in claim **1**, which comprises systemic administration 1-4 times per day or continuous administration in the amount of 0.01-100 μg/kg per day or a 13,14-dihydro-15-keto-16,16-difluoro-18-methyl-prostaglandin E_1 compound.

4. A method for treating as described in claim **2**, wherein the administration is in the amount of 0.1-10 μg/kg per day.

5. The method as described in claim 1, which comprises systemic administration 1-4 times per day or continuous administration at the amount of 0.01-100 μ g/kg per day.

6. The method as described in claim 5, wherein the administration is at the amount of 0.1-10 μg/kg per day.

7. A method for treating irritable bowel syndrome in a mammalian subject, which comprises administering an effective amount of 13,14-dihydro-15-keto-16,16-difluoro prostaglandin E_1 or a salt, ether, ester or amide thereof, to the subject.

8. The method as described in claim 7, which comprises administering an effective amount of 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E_1, or a pharmaceutically acceptable salt, ester or amide thereof.

9. The method for treating irritable bowel syndrome in a as described in claim 8, which comprises systemic administration 1-4 times per day or continuous administration in the amount of 0.01-100 μg/kg per day.

10. The method as described in claim 8, wherein the administration is in the amount of 0.1-10 μg/kg per day.

11. The method as described in claim 7, which comprises systemic administration 1-4 times per day or continuous administration at the amount of 0.01-100 μg/kg per day.

12. The method as described in claim 7, wherein the administration is at the amount of 0.1-10 μg/kg per day.

13. A method for treating abdominal discomfort associated with irritable bowel syndrome in a mammalian subject, which comprises administering an effective amount of 13,14-dihydro-15-keto-16,16-difluoro-18-methyl-prostaglandin E_1, or a salt, ether, ester or amide thereof, to the subject.

14. The method as described in claim 13, which comprises administering an effective amount of 13,14-dihydro-15-keto-16,16-difluoro-18-methyl-prostaglandin E_1, or a pharmaceutically acceptable salt, ester or amide thereof.

15. The method as described in claim 14, which comprises systemic administration 1-4 times per day or continuous administration in the amount of 0.01-100 μg/kg per day.

16. The method as described in claim 13, which comprises systemic administration 1-4 times per day or continuous administration in the amount of 0.01-100 μg/kg per day.

17. The method as described in claim 13, wherein the administration is in the amount of 0.1-10 μg/kg per day.

18. A method for treating abdominal discomfort associated with irritable bowel syndrome in a mammalian subject, which comprises administering an effective amount of 13,14-dihydro-15-keto-16,16-difluoro prostaglandin E_1, or a salt, ether, ester or amide thereof, to the subject.

19. The method as described in claim 18, which comprises administering an effective amount of 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E_1, or a pharmaceutically acceptable salt, ester or amide thereof.

20. The method as described in claim 19, which comprises systemic administration 1-4 times per day or continuous administration in the amount of 0.01-100 μg/kg per day.

21. The method as described in claim 18, which comprises systemic administration 1-4 times per day or continuous administration in the amount of 0.01-100 μg/kg per day.

22. The method as described in claim 18, wherein the administration is in the amount of 0.1-10 μg/kg per day.

* * * * *

Exhibit D

US006982283B2

(12) **United States Patent**
Ueno

(10) **Patent No.: US 6,982,283 B2**
(45) **Date of Patent: Jan. 3, 2006**

(54) **METHOD FOR TREATING DRUG-INDUCED CONSTIPATION**

(75) Inventor: **Ryuji Ueno**, Montgomery, MD (US)

(73) Assignee: **Sucampo AG**, Zug (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 217 days.

(21) Appl. No.: **10/135,397**

(22) Filed: **May 1, 2002**

(65) **Prior Publication Data**

US 2003/0073746 A1 Apr. 17, 2003

Related U.S. Application Data

(60) Provisional application No. 60/287,720, filed on May 2, 2001.

(51) **Int. Cl.**
A61K 31/557 (2006.01)
A61K 31/19 (2006.01)

(52) **U.S. Cl.** **514/530**; 514/531; 514/573

(58) **Field of Classification Search** 514/530, 514/531, 573
See application file for complete search history.

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Primary Examiner—Zohreh Fay
Assistant Examiner—Brian-Yong Kwon
(74) *Attorney, Agent, or Firm*—Sughrue Mion, PLLC

(57) **ABSTRACT**

Provided is a method for treating drug-induced constipation comprising a step of administering an effective amount of a 15-keto-prostaglaindin compound to a subject suffering from drug-induced constipation or a subject having a strong possibility of suffering from it. According to the present invention, a strong antagonistic action against drug-induced constipation can be obtained without substantially losing the main effect of the drug.

12 Claims, No Drawings

METHOD FOR TREATING DRUG-INDUCED CONSTIPATION

This application claims benefit to Provisional Application No. 60/287,720 filed May 2, 2001; the disclosure of which is incorporated herein by reference.

TECHNICAL FIELD

The present invention relates to a novel use of a 15-keto-prostaglandin compound for treating drug-induced constipation.

RELATED ART

Constipation is classified into functional constipation such as an atonic constipation, spastic constipation, rectal constipation, organic constipation such as caused by bowel disease and by stenosis due to postoperative adhesion, drug-induced constipation and the like.

Drug-induced constipation occurs as a side effect caused by using a drug. The drug may cause constipation not directly but indirectly. For example, constipation may be due to hard feces caused by fluid excretion outside the body with a diuretic. Further, it may be caused by an additive or synergistic effect of using plural drugs, each of which does not introduce constipation if administrated individually.

It is known that drugs causing constipation include narcotics used for controlling cancer pain (opioid-narcotic such as morphine and codeine), anticholinergic (such as antiparkinsonism drug, tricyclic and tetracyclic antidepressant and antiincontinence drug), antacid (such as aluminium preparation), bone weight increasing agent (such as calcium preparation), diuretic, iron preparation, calcium antagonist, benzodiazepine compound, phenotiazine compound (such as chlorpromazine), H_2-blocker, pill, tocopherol and the like.

For example, opioid such as morphine, which is one kind of narcotics, has a depressant action on the central nervous system (such as analgesic, antitussive, sedative or hypnotic action) and, since its analgesic action is extremely strong, it is effective for almost all pains including surgical and cancer pains. On the other hand, it exhibits a constipating action by affecting gastrointestine as a peripheral effect. Accordingly, when morphine is used for treating pain, almost all the patients applied with morphine constipate, and failure to control it will cause intractable constipation. Constipation is caused by administering the dose of morphine necessary for effecting analgesic action and it is hard to become tolerant, so that constipation continues as long as the administration of morphine by any route continues. For example, if morphine is applied to a cancer patient for relieving pain without taking sufficient steps for controlling constipation, it will become unable to continue the administration of morphine, thus degrading the therapeutic result of cancer pain relief. For this reason, during repetitious administration of morphine, it is very important to control constipation.

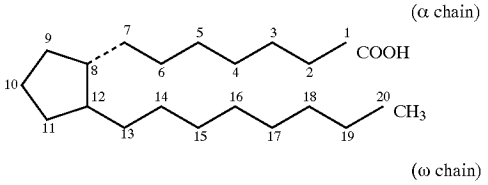
However, it has been reported that constipation induced by opioid such as morphine is not often sufficiently controlled by conventional cathartics (Twycross, R. G. et al.: Constipation. In: Control of alimentary symptoms in far advanced cancer. Edinburgh: Churchill Livingstone, 1986: 172–177, the cited references are herein incorporated by reference).

Recently, opioid antagonist such as naloxone has been tried to relax opioid-induced constipation at the sacrifice of analgesic action of opioid. It has been reported that use of opioid antagonist against opioid-induced constipation causes side effects such as return of pain and opioid withdrawal, which is contradict to the original purpose of the opioid administration (Culpepper-Morgan, J. A. et al.: NIDA Res. Monoger. 95: 399–400, 1989. and Clin. Pharmacol. Ther. 52: 90–95, 1992: Sykes, N. P.: Palliat-Med.10:135–144, 1996, the cited references are herein incorporated by reference).

Accordingly, it has been desired to develop a drug for relaxing drug-induced constipation without losing the main effect, for example, analgesic action of opioid such as morphine, of the drug.

Prostaglandins (hereinafter, referred to as PG(s)) are members of class of organic carboxylic acids, which are contained in tissues or organs of human or other mammals, and exhibit a wide range of physiological activity. PGs found in nature (primary PGs) generally have a prostanoic acid skeleton as shown in the formula (A):

(A)



On the other hand, some of synthetic analogues of primary PGs have modified skeletons. The primary PGs are classified to PGAs, PGBs, PGCs, PGDs, PGEs, PGFs, PGGs, PGHs, PGIs and PGJs according to the structure of the five-membered ring moiety, and further classified into the following three types by the number and position of the unsaturated bond at the carbon chain moiety:

Subscript 1: 13,14-unsaturated-15-OH

Subscript 2: 5,6- and 13,14-diunsaturated-15-OH

Subscript 3: 5,6-, 13,14-, and 17,18-triunsaturated-15-OH.

Further, the PGFs are classified, according to the configuration of the hydroxyl group at the 9-position, into α type (the hydroxyl group is of an α-configuration) and β type (the hydroxyl group is of a β-configuration).

PGE_1 and PGE_2 and PGE_3 are known to have vasodilatation, hypotension, gastric secretion decreasing, intestinal tract movement enhancement, uterine contraction, diuretic, bronchodilation and anti ulcer activities. $PGF_{1\alpha}$, $PGF_{2\alpha}$ and $PGF_{3\alpha}$ have been known to have hypertension, vasoconstriction, intestinal tract movement enhancement, uterine contraction, lutein body atrophy and bronchoconstriction activities.

In addition, some 15-keto PGs (i.e. those having an oxo group at position 15 in place of the hydroxy group) and 13,14-dihydro-15-keto-PGs are known as substances naturally produced by enzymatic reactions during in vivo metabolism of primary PGs. 15-keto PG compound have been disclosed in the specification of U.S. Pat. Nos. 5,073,569, 5,166,174, 5,221,763, 5,212,324 and 5,739,161 (These cited references are herein incorporated by reference).

The so-called primary PGs having hydroxy at the 15-position such as PGE_1, PGE_2 and the derivatives or analogs thereof are known to antagonize the enterogastric action of morphine (Christmas A. J.: Prostaglaindins 18, 279–284, 1979; B. J. Broughton: Prostaglaindins 22, 53–64, 1981, the cited references are herein incorporated by reference).

However, PGE_1 and PGE_2 are well known pain enhancing substances, which augment the action of bradykinin, a strong pain producing substance, and other pain producing substances. Accordingly, the so-called primary PGs having hydroxy at the 15-position have a possibility of affecting the analgesic action of opioid.

On the other hand, a 15-keto-16-halogen-PG compound is known to be useful as a cathartic (U.S. Pat. No. 5,317,032). However, it is not known at all how the 15-keto-PG compound affects the opioid-induced constipation or how it affects the main effect of a drug, e.g., the analgesic action of opioid.

SUMMARY OF THE INVENTION

The purpose of the present invention is to provide a composition for treating drug-induced constipation, which has a strong antagonistic action against drug-induced constipation without substantially losing the main effect of the drug.

As a result of a diligent research for biological activity of 15-keto-prostaglaindin compounds, the present inventor has found that a 15-keto-prostaglaindin compound has a superior antagonistic action against drug-induced constipation. Especially, because of its superior antagonistic action against opioid-induced constipation without affecting the analgesic action of opioid such as morphine on central nervous system, the compound has been found to be very useful for controlling opioid-induced constipation. Thus, the present invention has been completed.

Namely, the present invention relates to a composition for treating drug-induced constipation comprising a 15-keto-prostaglandin compound as an active ingredient.

The present invention also relates to a method for treating drug-induced constipation comprising a step of administering an effective amount of 15-keto-prostaglaindin compound to a subject suffering from drug-induced constipation or a subject having a strong possibility of suffering from it.

The present invention further relates to use of a 15-keto-prostaglaindin compound for manufacturing a pharmaceutical composition for treating drug-induced constipation.

DETAILED DESCRIPTION OF THE INVENTION

In the present invention, the "15-keto-prostaglandin compound" (hereinafter, referred to as "15-keto-PG compound") may include any of derivatives or analogs (including substituted derivatives) of a compound having an oxo group at 15-position of the prostanoic acid skeleton instead of the hydroxy group, irrespective of the configuration of the five-membered ring, the number of double bonds, presence or absence of a substituent, or any other modification in the α or ω chain.

The nomenclature of the 15-keto-PG compounds used herein is based on the numbering system of the prostanoic acid represented in the above formula (A).

The formula (A) shows a basic skeleton of the C-20 carbon atoms, but the 15-keto-PG compounds in the present invention are not limited to those having the same number of carbon atoms. In the formula (A), the numbering of the carbon atoms which constitute the basic skeleton of the PG compounds starts at the carboxylic acid (numbered 1), and carbon atoms in the α-chain are numbered 2 to 7 towards the five-membered ring, those in the ring are 8 to 12, and those in the ω-chain are 13 to 20. When the number of carbon atoms is decreased in the α-chain, the number is deleted in the order starting from position 2; and when the number of carbon atoms is increased in the α-chain, compounds are named as substitution compounds having respective substituents at position 2 in place of the carboxy group (C-1). Similarly, when the number of carbon atoms is decreased in the ω-chain, the number is deleted in the order starting from position 20; and when the number of carbon atoms is increased in the ω-chain, the carbon atoms beyond position 20 are named as substituents. Stereochemistry of the compounds is the same as that of the above formula (A) unless otherwise specified.

In general, each of the terms PGD, PGE and PGF represents a PG compound having hydroxy groups at positions 9 and/or 11, but in the present specification, these terms also include those having substituents other than the hydroxy group at positions 9 and/or 11. Such compounds are referred to as 9-dehydroxy-9-substituted-PG compounds or 11-dehydroxy-11-substituted-PG compounds. A PG compound having hydrogen in place of the hydroxy group is simply named as 9- or 11-dehydroxy compound.

As stated above, the nomenclature of the 15-keto-PG compounds is based on the prostanoic acid skeleton. However, in case the compound has a similar partial construction as a prostaglandin, the abbreviation of "PG" may be used. Thus, a PG compound of which α-chain is extended by two carbon atoms, that is, having 9 carbon atoms in the α-chain is named as 2-decarboxy-2-(2-carboxyethyl)-15-keto-PG compound. Similarly, a PG compound having 11 carbon atoms in the α-chain is named as 2-decarboxy-2-(4-carboxybutyl)-15-keto-PG compound. Further, a PG compound of which ω-chain is extended by two carbon atoms, that is, having 10 carbon atoms in the ω-chain is named as 15-keto-20-ethyl-PG compound. These compounds, however, may also be named according to the IUPAC nomenclatures.

The 15-keto-PGs used in the present invention may include any PG derivatives or analogs insofar as having an oxo group at position 15 in place of the hydroxy group. Accordingly, for example, a 15-keto-PG type 1 compound having a double bond at 13–14 position, a 15-keto-PG type 2 compound having two double bond at 13–14 and 5–6 position, a 15-keto-PG type 3 compound having three double bond at 5–6, 13–14 and 17–18 position, 13,14-dihydro-15-keto-PG compound wherein the double bond at 13–14 position is single bond.

Typical examples of the compounds used in the present invention include 15-keto-PG type 1, 15-keto-PG type 2, 15-keto-PG type 3, 13,14-dihydro-15-keto-PG type 1, 13,14-dihydro-15-keto-PG type 2, 13,14-dihydro-15-keto-PG type 3 and the derivatives or analogs thereof.

Examples of the analogs (including substituted derivatives) or derivatives include a 15-keto-PG compound of which carboxy group at the end of α-chain is esterified; a compound of which α-chain is extended; physiologically acceptable salt thereof; a compound having a double bond at 2–3 position or a triple bond at position 5–6, a compound having substituent(s) at position 3, 5, 6, 16, 17, 18, 19 and/or 20; and a compound having lower alkyl or a hydroxy (lower) alkyl group at position 9 and/or 11 in place of the hydroxy group.

According to the present invention, preferred substituents at position 3, 17, 18 and/or 19 include alkyl having 1–4 carbon atoms, especially methyl and ethyl. Preferred substituents at position 16 include lower alkyl such as methyl and ethyl, hydroxy, halogen atoms such as chlorine and fluorine, and aryloxy such as trifluoromethylphenoxy. Pre-

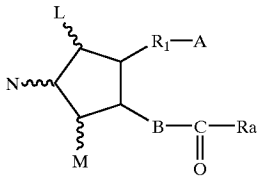
ferred substituents at position 17 include lower alkyl such as methyl and ethyl, hydroxy, halogen atoms such as chlorine and fluorine, aryloxy such as trifluoromethylphenoxy. Preferred substituents at position 20 include saturated or unsaturated lower alkyl such as C1–4 alkyl, lower alkoxy such as C1–4 alkoxy, and lower alkoxy alkyl such as C1–4 alkoxy-C1–4 alkyl. Preferred substituents at position 5 include halogen atoms such as chlorine and fluorine. Preferred substituents at position 6 include an oxo group forming a carbonyl group. Stereochemistry of PGs having hydroxy, lower alkyl or hydroxy(lower)alkyl substituent at position 9 and/or 11 may be α, β or a mixture thereof.

Further, the above analogs or derivatives may be compounds having an alkoxy, cycloalkyl, cycloalkyloxy, phenoxy or phenyl group at the end of the ω-chain where the chain is shorter than the primary PGs.

Especially preferred compounds include a 13,14-dihydro-15-keto-PG compound which has a single bond at position 13–14; a 15-keto-16 mono or di-halogen PG compound which has one or two halogen atoms such as chlorine and fluorine at position 16; and a 15-keto-PGE compound which has an oxo group at position 9 and a hydroxyl group at position 11 of the five membered ring.

A preferred compound used in the present invention is represented by the formula (I):

(I)



wherein

L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is —CH_2OH, —$COCH_2OH$, —COOH or a functional derivative thereof;

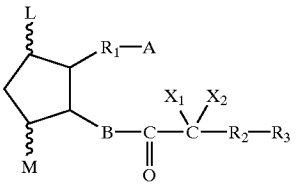
B is —CH_2—CH_2—, —CH═CH— or —C≡C—;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

Ra is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or hetrocyclic-oxy group; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclic-oxy group.

A group of particularly preferable compounds among the above-described compounds is represented by the formula (II):

(II)



wherein L and M are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is —CH_2OH, —$COCH_2OH$, —COOH or a functional derivative thereof;

B is —CH_2—CH_2—, —CH═CH—, —C≡C—;

X_1 and X_2 are hydrogen, lower alkyl, or halogen;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur;

R_2 is a single bond or lower alkylene; and

R_3 is lower alkyl, lower alkoxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclic-oxy group.

In the above formula, the term "unsaturated" in the definitions for R_1 and Ra is intended to include at least one or more double bonds and/or triple bonds that are isolatedly, separately or serially present between carbon atoms of the main and/or side chains. According to the usual nomenclature, an unsaturated bond between two serial positions is represented by denoting the lower number of the two positions, and an unsaturated bond between two distal positions is represented by denoting both of the positions.

The term "lower or medium aliphatic hydrocarbon" refers to a straight or branched chain hydrocarbon group having 1 to 14 carbon atoms (for a side chain, 1 to 3 carbon atoms are preferable) and preferably 1 to 10, especially 6 to 10 carbon atoms for R_1 and 1 to 10, especially 1 to 8 carbon atoms for R_a.

The term "halogen" covers fluorine, chlorine, bromine and iodine.

The term "lower" throughout the specification is intended to include a group having 1 to 6 carbon atoms unless otherwise specified.

The term "lower alkyl" refers to a straight or branched chain saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl.

The term "lower alkylene" refers to a straight or branched chain bivalent saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methylene, ethylene, propylene, isopropylene, butylene, isobutylene, t-butylene, pentylene and hexylene.

The term "lower alkoxy" refers to a group of lower alkyl-O-, wherein lower alkyl is as defined above.

The term "hydroxy(lower)alkyl" refers to a lower alkyl as defined above which is substituted with at least one hydroxy group such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 1-methyl-l-hydroxyethyl.

The term "lower alkanoyloxy" refers to a group represented by the formula RCO—O—, wherein RCO— is an acyl group formed by oxidation of a lower alkyl group as defined above, such as acetyl.

The term "cyclo(lower)alkyl" refers to a cyclic group formed by cyclization of a lower alkyl group as defined above but contains three or more carbon atoms, and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cyclo(lower)alkyloxy" refers to the group of cyclo(lower)alkyl-O-, wherein cyclo(lower)alkyl is as defined above.

The term "aryl" may include unsubstituted or substituted aromatic hydrocarbon rings (preferably monocyclic groups), for example, phenyl, tolyl, and xylyl. Examples of the substituents are halogen atom and halo(lower)alkyl, wherein halogen atom and lower alkyl are as defined above.

The term "aryloxy" refers to a group represented by the formula ArO—, wherein Ar is aryl as defined above.

The term "heterocyclic group" may include mono- to tri-cyclic, preferably monocyclic heterocyclic group which is 5 to 14, preferably 5 to 10 membered ring having optionally substituted carbon atom and 1 to 4, preferably 1 to 3 of 1 or 2 types of hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom. Examples of the heterocyclic group include furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, 2-pyrrolinyl, pyrrolidinyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, piperidino, piperazinyl, morpholino, indolyl, benzothienyl, quinolyl, isoquinolyl, purinyl, quinazolinyl, carbazolyl, acridinyl, phenanthridinyl, benzimidazolyl, benzimidazolonyl, benzothiazolyl, phenothiazinyl. Examples of the substituent in this case include halogen, and halogen substituted lower alkyl group, wherein halogen atom and lower alkyl group are as described above.

The term "heterocyclic-oxy group" means a group represented by the formula HcO—, wherein Hc is a heterocyclic group as described above.

The term "functional derivative" of A includes salts (preferably pharmaceutically acceptable salts), ethers, esters and amides.

Suitable "pharmaceutically acceptable salts" include conventionally used non-toxic salts, for example a salt with an inorganic base such as an alkali metal salt (such as sodium salt and potassium salt), an alkaline earth metal salt (such as calcium salt and magnesium salt), an ammonium salt; or a salt with an organic base, for example, an amine salt (such as methylamine salt, dimethylamine salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino) ethane salt, monomethylmonoethanolamine salt, procaine salt and caffeine salt), a basic amino acid salt (such as arginine salt and lysine salt), tetraalkyl ammonium salt and the like. These salts may be prepared by a conventional process, for example from the corresponding acid and base, or by salt interchange.

Examples of the ethers include alkyl ethers, for example, lower alkyl ethers such as methyl ether, ethyl ether, propyl ether, isopropyl ether, butyl ether, isobutyl ether, t-butyl ether, pentyl ether and 1-cyclopropyl ethyl ether; and medium or higher alkyl ethers such as octyl ether, diethylhexyl ether, lauryl ether and cetyl ether; unsaturated ethers such as oleyl ether and linolenyl ether; lower alkenyl ethers such as vinyl ether, allyl ether; lower alkynyl ethers such as ethynyl ether and propynyl ether; hydroxy(lower)alkyl ethers such as hydroxyethyl ether and hydroxyisopropyl ether; lower alkoxy (lower)alkyl ethers such as methoxymethyl ether and 1-methoxyethyl ether; optionally substituted aryl ethers such as phenyl ether, tosyl ether, t-butylphenyl ether, salicyl ether, 3,4-di-methoxyphenyl ether and benzamidophenyl ether; and aryl(lower)alkyl ethers such as benzyl ether, trityl ether and benzhydryl ether.

Examples of the esters include aliphatic esters, for example, lower alkyl esters such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester and 1-cyclopropylethyl ester; lower alkenyl esters such as vinyl ester and allyl ester; lower alkynyl esters such as ethynyl ester and propynyl ester; hydroxy(lower)alkyl ester such as hydroxyethyl ester; lower alkoxy (lower) alkyl esters such as methoxymethyl ester and 1-methoxyethyl ester; and optionally substituted aryl esters such as, for example, phenyl ester, tolyl ester, t-butylphenyl ester, salicyl ester, 3,4-di-methoxyphenyl ester and benzamidophenyl ester; and aryl(lower)alkyl ester such as benzyl ester, trityl ester and benzhydryl ester.

The amide of A means a group represented by the formula —CONR'R", wherein each of R' and R" is hydrogen, lower alkyl, aryl, alkyl- or aryl-sulfonyl, lower alkenyl and lower alkynyl, and include for example lower alkyl amides such as methylamide, ethylamide, dimethylamide and diethylamide; arylamides such as anilide and toluidide; and alkyl- or aryl-sulfonylamides such as methylsulfonylamide, ethylsulfonyl-amide and tolylsulfonylamide.

Preferred examples of L and M include hydroxy and oxo, and especially, M is hydroxy and L is oxo which has a 5-membered ring structure of, so called, PGE type.

Preferred example of A is —COOH, its pharmaceutically acceptable salt, ester or amide thereof.

Preferred example of B is —CH_2—CH_2—, which provide the structure of so-called, 13,14-dihydro type.

Preferred example of X_1 and X_2 is that at least one of them is halogen, more preferably, both of them are halogen, especially, fluorine that provides a structure of, so called 16,16-difluoro type.

Preferred R_1 is a hydrocarbon containing 1–10 carbon atoms, preferably, 6–10 carbon atoms. Further, at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur.

Examples of R_1 include, for example, the following groups:

—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH═CH—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH═CH—,
—CH_2—C≡C—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—$CH(CH_3)$—CH_2—
—CH_2—CH_2—CH_2—CH_2—O—CH_2—,
—CH_2—CH═CH—CH_2—O—CH_2—,
—CH_2—C≡C—CH_2—O—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH═CH—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—CH═CH—,
—CH_2—C≡C—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—$CH(CH_3)$—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH═CH—CH_2—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH═CH—,
—CH_2—C≡C—CH_2—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—$CH(CH_3)$—CH_2—

Preferred Ra is a hydrocarbon containing 1–10 carbon atoms, more preferably, 1–8 carbon atoms. Ra may have one or two side chains having one carbon atom.

The configuration of the ring and the α- and/or ω chains in the above formula (I) and (II) may be the same as or different from that of the primary PGs. However, the present invention also includes a mixture of a compound having a primary type configuration and a compound of a non-primary type configuration.

The Examples of the typical compound in the invention are 13,14-dihydro-15-keto-16-mono or difluoro-PGE compound, the derivatives or analogs thereof.

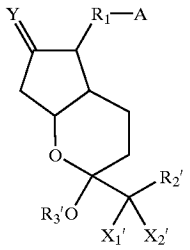
The 15-keto-PG compound of the present invention may be in the keto-hemiacetal equilibrium by formation of a hemiacetal between hydroxy at position 11 and oxo at position 15.

For example, it has been revealed that when both of X_1 and X_2 are halogen atoms, especially, fluorine atoms, the compound contains a tautomeric isomer, bicyclic compound.

If such tautomeric isomers as above are present, the proportion of both tautomeric isomers varies with the structure of the rest of the molecule or the kind of the substituent present. Sometimes one isomer may predominantly be present in comparison with the other. However, it is to be appreciated that the 15-keto-PG compounds used in the invention include both isomers.

Further, the 15-keto-PG compounds used in the invention include the bicyclic compound and analogs or derivatives thereof. The bicyclic compounds is represented by the formula (III)

(III)



wherein, A is —CH_2OH, —$COCH_2OH$, —COOH or a functional derivative thereof;

X_1' and X_2' are hydrogen, lower alkyl, or halogen;

Y is

R_4' and R_5' are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R_4' and R_5' are not hydroxy and lower alkoxy at the same time.

R_1 is a divalent saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

Ra' is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower) alkyloxy, aryl, aryloxy, heterocyclic group or hetrocyclic-oxy group; cyclo(lower)alkyl; cyclo(lower) alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclic-oxy group.

R_3' is hydrogen, lower alkyl, cyclo(lower)alkyl, aryl or heterocyclic group.

Further more, while the compounds used in the invention may be represented by a structure formula or name based on keto-type regardless of the presence or absence of the isomers, it is to be noted that such structure or name does not intend to exlclude the hemiacetal type compound.

In the present invention, any of isomers such as the individual tautomeric isomers, the mixture thereof, or optical isomers, the mixture thereof, a racemic mixture, and other steric isomers may be used in the same purpose.

Some of the compounds used in the present invention may be prepared by the method disclosed in U.S. Pat. Nos. 5,073,569, 5,166,174, 5,221,763, 5,212,324 and 5,739,161 and 6,242,485.

(these cited references are herein incorporated by reference)

The subject to be treated by the present invention may be any mammalian subject including animals and human beings. According to the method of the present invention, a pharmaceutical composition comprising a 15-keto-prostaglandin composition as an active ingredient may be administrated either systemically or topically.

Usually, the composition is administered by oral administration, intravenous injection (including infusion), subcutaneous injection, intra rectal administration, intra vaginal administration and the like. The dose of the active ingredient may vary depending on the strain i.e. particular animal or human, age, sex, body weight of the patient to be treated, symptom to be treated, desired therapeutic effect, administration route, term of treatment and the like.

Typically, a satisfactory effect can be obtained by systemic administration 1–4 times per day or continuous administration of the 15-keto-prostaglandin compound at the amount of 0.00001–100 mg/kg per day.

The composition of the present invention can be formulated as a composition for oral administration, for injection, for perfusion or for external administration, tablet, sublingual, suppository, and vaginal suppository.

The composition of the present invention may further contain physiologically acceptable additives. Said additives may include the ingredients used with the 15-keto-PG compound such as excipient, diluent, filler, resolvent, lubricant, adjuvant, binder, disintegrator, coating agent, cupsulating agent, ointment base, suppository base, aerozoling agent, emulsifier, dispersing agent, suspending agent, thickener, tonicity agent, buffering agent, soothing agent, preservative, antioxidant, corrigent, flavor, colorant, a functional material such as cyclodextrin and biodegradable polymer, stabilizer. The additives may be selected from those described in general reference books of pharmaceutics.

The amount of the 15-keto-prostaglandin compound contained in a composition may vary depending on the formulation of the composition, and may generally be 0.0001–10.0 wt %, more preferably 0.001–1.0 wt %.

Examples of solid compositions for oral administration include tablets, troches, sublingual tablets, capsules, pills, powders, granules and the like. The solid composition may be prepared by mixing one or more active ingredients with at least one inactive diluents. The composition may further contain additives other than the inactive diluents, for example, a lubricant, a disintegrator and a stabilizer. Tablets and pills may be coated with an enteric or gastroenteric film, if necessary. They may be covered with two or more layers.

They may also be adsorbed to a sustained release material, or microcapsulated. Additionally, the compositions may be capsulated by means of an easily degradable material such gelatin. They may be further dissolved in a appropriate solvent such as fatty acid or its mono, di or triglyceride to be a soft capsule. Sublingual tablet may be used in need of fast-acting property.

Examples of liquid compositions for oral administration include emulsions, solutions, suspensions, syrups and elixirs and the like. Said composition may further contain a conventionally used inactive diluents e.g. purified water or ethyl alcohol. The composition may contain additives other than the inactive diluents such as adjuvant e.g. wetting agents and suspending agents, sweeteners, flavors, fragrance and preservatives.

The composition of the present invention may be in the form of spraying composition which contains one or more active ingredients and may be prepared according to a known method.

Example of the injectable compositions of the present invention for parenteral administration include sterile aqueous or nonaqueous solutions, suspensions and emulsions comprising one or more active ingredient. Diluents for the aqueous solution or suspension may include, for example, distilled water for injection, physiological saline and Ringer's solution. Non-aqueous diluents for solution and suspension may include, for example, propylene glycol, polyethylene glycol, vegetable oils such as olive oil, alcohols such as ethanol and polysorbate. The composition may further comprise additives such as preservatives, wetting agents, emulsifying agents, dispersing agents and the like. They may be sterilized by filtration through, e.g. a bacteria-retaining filter, compounding with a sterilizer, or by means of gas or radioisotope irradiation sterilization. The injectable composition may also be provided as a sterilized powder composition to be dissolved in a sterilized solvent for injection before use.

Another formulation of the composition according to the present invention may be rectal or vaginal suppository. Said suppository may be prepared by mixing at least one active compound according to the present invention with a suppository base e.g. cacao butter and may optionally be admixed with a nonionic surfactant having a suitable softening temperature to improve absorption.

The term "treatment" or "treating" used herein includes any means of control such as prevention, care, relief of the condition, attenuation of the condition and arrest of progression.

The term "drug-induced constipation" used herein is not limited to a particular constipation condition so far as the condition is caused by using a drug as its side effect, which also includes secondary constipation due to the drug use. Further, constipation caused by an additive or synergistic effect due to combined drug administration is also included.

Drugs which cause drug-induced constipation to be treated by the present invention may include, for example, opioids of narcotic drugs such as morphine (such as morphine hydrocholoride and MS contin) and codeine (such as codeine phosphate); anticholineric agents such as antiparkinsonism drugs (trihexyphenidyl and levodopa), antidepressants (tricyclic antidepressants such as amoxapine, trimipramine, aminotriptyline, imipramine, clomipramine, dosulepin, nortriptyline and lofepramine, tetracyclic antidepressants such as setiptiline, maprotiline and mianserin) and anti-incontinence agents (such as propanetheline and oxybutynin); antacids (such as alminium preparation), bone weight increasing agents (such as calcium preparations), diuretic, iron preparations, calcium antagonist, benzodiazepine drugs, phenothiazine drugs (such as chlorpromazine), H_2-blockers, pill, tocopherol. Especially, constipation conditions induced by opioid such as morphine and codeine, and antidepressants such as tricyclic antidepressants including imipramine are effectively treated 0with the composition of the present invention.

In the present invention, "a subject suffering from drug-induced constipation or a subject having a strong possibility of suffering from it" includes both a subject actually constipating due to the administration of a drug which causes constipation and a subject having a strong possibility of constipating due to the administration of a drug, for example, a subject being administered with a drug such as an opioid or an antidepressant, that is known to have a strong possibility of constipation as a side effect.

In the present invention, a dosage form may include one active ingredient only or a combination of two or more active ingredients. When a combination of a plurality of active ingredients are used, their respective contents can be suitably increased or decreased in consideration of their effects and safety.

The composition of, the present invention can further include other pharmacologically active ingredients as far as they do not contradict the purpose of the present invention.

The further details of the present invention will follow with reference to test examples, which, however, are not intended to limit the present invention.

EXAMPLE 1

Antagonism to Morphine-Induced Constipation

Male ICR mice were fasted overnight in wire-bottomed cages to prevent coprophagia, and 15 mice were used for each group. Morphine hydrochloride (Takeda Chemical Industries, Ltd., Osaka Japan) was injected intraperitoneally to animals at 5 mg/kg. Immediately after the morphine-injection, 0.1 mL graphite marker (2:1 mixture of Pilot INK-30-B and 10% tragacanth mucilage) and 5 mL/Kg vehicle (physiological saline containing 0.01% polysorbate 80 and 0.5% ethanol) or 1, 10, or 100 μg/kg test substance (13,14-dihydro-15-keto-16,16-difluoro-PGE_1) in 5 mL/Kg of the vehicle were administered orally. A normal control group received graphite marker and vehicle orally in the above volumes without the morphine-injection. One hundred and fifty minutes after the administration of graphite marker, animals were sacrificed by cervical dislocation, and examined the caecum for the presence of graphite marker. It was judged as a positive response when graphite marker was found in the caecum (positive score).

The number of animals in which graphite marker was found in the caecum (number of animals with positive scores) and its ratio in each group are shown in Table 1.

TABLE 1

Group	Number of animals with positive scores[a]/ Number of animals tested	Ratio of animals with positive scores
Normal (vehicle)	15/15**	100%
Morphine + vehicle	3/15	20%
Morphine + test substance		
1 μg/kg	9/15*	60%
10 μg/kg	13/15**	87%
100 μg/kg	14/15**	93%

[a]Positive score: Presence of graphite marker in the caecum
*$p < 0.05$,
**$p < 0.01$ compared with morphine + vehicle group (χ^2 test)

In the normal group, graphite marker was found in the caecum in all the 15 animals (100%).

In the morphine+vehicle group, graphite marker was found in the caecum in 3 out of 15 animals (20%). The

number of positive animals in the morphine+vehicle group was significantly decreased as compared with that of the normal group, which indicated that constipation was induced by the morphine treatment.

In the groups received test substance at 1, 10 or 100 μg/kg immediately after the morphine administration, graphite marker was found dose-dependently in the caecum in 9 (60%), 13 (87%) and 14 (93%) out of 15 animals, respectively. The test substance group significantly antagonized the morphine-induced constipation as compared with control (morphine+vehicle) group.

Above results demonstrate that the substances of the present invention antagonize the opioid-induced constipation even at a low dose of 1 μg/kg.

EXAMPLE 2 (COMPARATIVE EXAMPLE)

Antagonism to Morphine-Induced Constipation

The effects of conventional cathartics (sennoside and sodium picosulfate) clinically used for the treatment of constipation in the patients applied with morphine on morphine-induced constipation were evaluated.

Sennoside (tablets: Novartis Pharma K.K., Tokyo, Japan) were crushed with mortar and ground into fine powder, and suspended in 0.5% tragacanth solution to yield proper concentration for the intended dose level of administration. Sodium picosulfate (liquid: Teijin K.K., Tokyo, Japan) was diluted with physiological saline solution.

Dosage levels of each test substance were set at 1 and 10 times of clinical daily dosage (clinical daily dosage: sennoside 24 mg, sodium picosulfate 7.5 mg; assuming body weight is 50 kg, they are equivalent to 0.48 mg/kg and 0.15 mg/kg, respectively). Each diluent for test substance was used as a vehicle.

The experimental procedure was the same as described in example 1.

The number of animals in which graphite marker was found in the caecum (number of animals with positive scores) and its ratio in each group are shown in Table 2 (sennoside) and Table 3 (sodium picosulfate).

TABLE 2

Group	Number of animals with positive scores[a]/ Number of animals tested	Ratio of animals with positive scores
Normal (vehicle)	10/10**	100%
Morphine + vehicle	2/10	20%
Morphine + sennoside		
0.48 mg/kg	2/10	20%
4.8 mg/kg	2/10	20%

[a]Positive score: Presence of graphite marker in the caecum
**p < 0.01 compared with morphine + vehicle group (χ^2 test)

TABLE 3

Group	Number of animals with positive scores[a]/ Number of animals tested	Ratio of animals with positive scores
Normal (vehicle)	8/10*	80%
Morphine + vehicle	3/10	30%
Morphine + sodium picosulfate		
0.15 mg/kg	3/10	30%
1.5 mg/kg	4/10	40%

[a]Positive score: Presence of graphite marker in the caecum
*p < 0.05 compared with morphine + vehicle group (χ^2 test)

The cathartics (sennoside and sodium picosulfate) conventionally used for the treatment of constipation in patients applied with morphine had no effect on morphine-induced constipation at the clinical daily dosage and even at 10 times of the clinical daily dosage.

Above results demonstrate that conventional cathartics, which have purgative action, does not necessarily antagonize opioid-induced constipation, and suggests that the conventional cathartics are hard to control constipation sufficiently.

EXAMPLE 3

Effect on Analgesic Action

Male ICR mice were fasted overnight in wire-bottomed cages to prevent coprophagia. The tail of the animal was pinched with clamp forceps, and the response time from the tail-pinch to fierce striking, biting or crying was measured. 18 mice whose response time of 2 second or shorter were used as test animals. Morphine hydrochloride (Takeda Chemical Industries, Ltd., Osaka, Japan) was injected intraperitoneally to the animals at 5 mg/kg. Immediately after the morphine-injection, vehicle (physiological saline containing 0.01% polysorbate 80 and 0.5% ethanol) or 1, 10, or 100 μg/kg test substance (13,14-dihydro-15-keto-16,16-difluoro-PGE_1) dissolved in the vehicle was administered orally in an administration volume of 5 mL/kg. The animals of normal control group received vehicle orally in the above volume without morphine-injection.

The response time of each animal following tail-pinch was measured 30, 60, 90, 120 and 150 minutes after the administration. If a mouse took longer than 10 seconds to respond, measurement was stopped to avoid injuring the tail tissue, and the response time was recorded as 10 second. Results are shown in Table 4.

TABLE 4

Group	Number of animals	Response time, mean ± S.E., sec. Before administration	Time after administration 30 min	60 min	90 min	120 min	150 min
Normal (vehicle)	18	0.9 ± 0.1	1.0 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.3 ± 0.1
Morphine + vehicle	18	1.0 ± 0.1	2.8 ± 0.6**	1.9 ± 0.3*	1.8 ± 0.4^{+}	1.4 ± 0.2	1.2 ± 0.1
Morphine + test substance							
1 μg/kg	18	1.0 ± 0.1	3.2 ± 0.7**	2.3 ± 0.6^{+}	1.5 ± 0.2*	1.3 ± 0.1	1.3 ± 0.1
10 μg/kg	18	1.0 ± 0.1	3.4 ± 0.5**	1.8 ± 0.2**	1.4 ± 0.1*	1.3 ± 0.1	1.2 ± 0.1
100 μg/kg	18	1.0 ± 0.1	2.9 ± 0.6**	1.8 ± 0.3*	1.5 ± 0.1*	1.2 ± 0.1	1.3 ± 0.1

$^{+}p < 0.1$,
$^{*}p < 0.05$,
$^{**}p < 0.01$ compared with normal group (Student's t-test)
No significant difference between Morphine + vehicle group and each Morphine + test substance group (Student's t-test)

The response times before the administration were about 1 second in all the groups, and no difference was found among the groups.

In the normal group, the response time at every measurement time after the vehicle administration was not different from that of before the administration.

In the morphine+vehicle group, a significant increase in the response time was found 30 and 60 minutes after the morphine-treatment as compared with that of the normal group. The tendency for the increase of the response time was still found 90 minutes after the morphine-treatment. The analgesic effect of morphine was almost completely disappeared 120 and 150 minutes after the morphine-treatment.

In each morphine+test substance group, significant increase of response time was observed as compared with that of the normal group. In the morphine+test substance groups, the response times were similar to those observed in the morphine+vehicle group.

No significant difference in the response time was found between the morphine+vehicle group and the morphine+test substance groups, which indicates that test substance did not affect the analgesic action of morphine.

Above results demonstrates that the substances of the present invention does not affect the analgesic action of opioid even at a high dose of 100 μg/kg.

EXAMPLE 4

Antagonism to Imipramine (A Tricyclic Antidepressant)-Induced Constipation

Male ICR mice were fasted overnight in wire-bottomed cages to prevent coprophagia, and 10 mice were used for each group. Imipramine hydrochloride (Wako Pure Chemical Industries, Ltd., Osaka, Japan) at 60 mg/kg was injected intraperitoneally to the animals. Immediately after the imipramine-injection, 0.1 mL of carbon marker (10% carbon powder suspension in 5% gum Arabic) and vehicle (physiological saline solution containing 0.01% polysorbate 80 and 0.5% ethanol) or test substance (13,14-dihydro-15-keto-16,16-difluoro-PGE_1) in an administration volume of 5 mL/kg were orally administered. A normal control group received carbon marker and vehicle in the above volume orally without the imipramine-injection. One hundred and fifty minutes after the administration of carbon marker, animals were sacrificed by cervical dislocation, and examined the caecum for the presence of carbon marker. It was judged as a positive response when carbon marker was found in the caecum (positive scores).

The number of animals in which carbon marker was found in the caecum (number of animals with positive scores) and its ratio in each group are shown in Table 5.

These results demonstrate that the substance of the present invention antagonize the imipramine-induced constipation.

TABLE 5

Group	Number of animals with positive scores[a]/ Number of animals tested	Ratio of animals with positive scores
Normal (vehicle)	9/10**	90%
Imipramine + vehicle	1/10	10%
Imipramine + test substance 10 μg/kg	3/10	30%
Imipramine + test substance 100 μg/kg	7/10**	70%

[a]Positive score: Presence of carbon marker in the caecum
**P < 0.01 compared with imipramine + vehicle group (χ^2 test)

EXAMPLE 5 (COMPARATIVE EXAMPLE)

Antagonism to Imipramine (A Tricyclic Antidepressant)-Induced Constipation

The effect to the imipramine-induced constipation was evaluated on the cathartic (sennoside) clinically used for the treatment of the constipation in patients. Preparation and dose levels of sennoside were the same as described in example 2. The experimental procedure was the same as described in example 4.

The number of animals in which carbon marker was found in the caecum (number of animals with positive scores) and its ratio in each group are shown in Table 6.

These results demonstrate that sennoside has no effect on the imipramine-induced constipation.

TABLE 6

Group	Number of animals with positive scores[a]/ Number of animals tested	Ratio of animals with positive scores
Normal (vehicle)	7/10**	70%
Imipramine + vehicle	1/10	10%
Imipramine + sennoside 0.48 μg/kg	2/10	20%

TABLE 6-continued

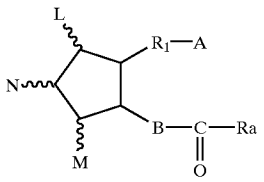
Group	Number of animals with positive scores[a)]/ Number of animals tested	Ratio of animals with positive scores
Imipramine + sennoside 4.8 μg/kg	2/10	20%

[a)]Positive score: Presence of carbon marker in the caecum
**P < 0.01 compared with imipramine + vehicle group (χ^2 test)

What is claimed is:

1. A method for treating drug-induced constipation comprising a step of administering an effective amount of 15-keto-prostaglandin compound to a subject suffering from drug-induced constipation or in need thereof of such treatment, wherein the 15-keto-prostaglandin compound is one represented by formula (I):

(I)



wherein

L,M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is —CH_2OH, —$COCH_2OH$, —COOH or a functional derivative thereof;

B is —CH_2—CH_2—, —CH═CH— or —C≡C—;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group and at least one carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

Ra is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclic-oxy group; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclic-oxy group.

2. The method of claim **1**, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-prostaglandin compound.

3. The method of claim **1**, wherein the 15-keto-prostaglandin compound is a 15-keto-16-mono- or di-halogen-prostaglandin compound.

4. The method of claim **1**, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16-mono- or di-halogen-prostaglandin compound.

5. The method of claim **2**, wherein the 15-keto-prostaglandin compound is a 15-keto-16-mono- or di-fluoro-prostaglandin compound.

6. The method of claim **2**, wherein the 15-keto prostaglandin compound is a 13,14-dihydro-15-keto-16-mono- or di-fluoro-prostaglandin compound.

7. The method of claim **2**, wherein the 15-keto-prostaglandin compound is a 15-keto-prostaglandin E compound.

8. The method of claim **2**, wherein the 15-keto-prostaglandin compound is 13,14-dihydro-15-keto-16, 16-difluoro-prostaglandin E_1.

9. The method of claim **2**, wherein the drug inducing constipation is an opioid compound.

10. The method of claim **9**, wherein the opioid compound is a morphine compound or a codeine compound.

11. The method of claim **1**, wherein the drug inducing constipation is an anticholinergic drug.

12. The method of claim **11**, wherein the anticholinergic drug is a tricyclic antidepressant.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,982,283 B2
APPLICATION NO. : 10/135397
DATED : January 3, 2006
INVENTOR(S) : Ryuji Ueno

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the cover page of the patent, under "(56) **References Cited**", please include the following references considered by the Examiner:

For "U.S. PATENT DOCUMENTS", please insert the following:

4,158,062	6/1979	Caton et al.
5,164,415 A	11/1992	Ueno

For "FOREIGN PATENT DOCUMENTS", please insert the following:

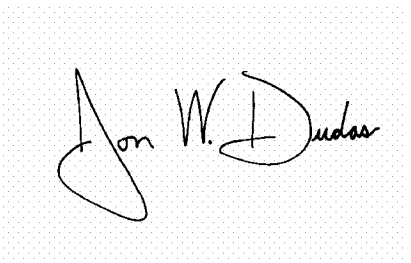
EP	0 310 305 A2	4/1989
EP	0 424 156 A2	4/1991
JP	2-32055 A	2/1990

For "OTHER PUBLICATIONS", please insert the following:

Dajani, E.Z. II et al., "Effects of E Prostaglandins, Diphenoxylate and Morphine on Intestinal Motility In Vivo", European Journal of Pharmacology, Vol. 34, No. 1, 1975, pages 105-113

Signed and Sealed this

Sixth Day of February, 2007



JON W. DUDAS
Director of the United States Patent and Trademark Office

Exhibit E

US008097653B2

(12) **United States Patent**
Ueno et al.

(10) **Patent No.: US 8,097,653 B2**
(45) **Date of Patent: *Jan. 17, 2012**

(54) **DOSAGE UNIT COMPRISING A PROSTAGLANDIN ANALOG FOR TREATING CONSTIPATION**

(75) Inventors: **Ryuji Ueno**, Montgomery, MD (US); **Myra L. Patchen**, Fairfax, VA (US)

(73) Assignee: **Sucampo AG**, Zug (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/293,516**

(22) Filed: **Nov. 14, 2002**

(65) **Prior Publication Data**

US 2003/0119898 A1 Jun. 26, 2003

Related U.S. Application Data

(60) Provisional application No. 60/331,316, filed on Nov. 14, 2001.

(51) **Int. Cl.**
A61K 31/557 (2006.01)
A61K 31/35 (2006.01)

(52) **U.S. Cl.** **514/573**; 514/456

(58) **Field of Classification Search** 514/456, 514/460, 892, 211, 573

See application file for complete search history.

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Primary Examiner — Sreeni Padmanabhan
Assistant Examiner — Gigi Huang
(74) *Attorney, Agent, or Firm* — Sughrue Mion, PLLC

(57) **ABSTRACT**

A dosage unit for treating constipation in a human patient is described. The dosage unit of the invention comprises a halogenated prostaglandin analog and a pharmaceutically suitable excipient. The dosage unit relieves constipation without substantial side effects.

7 Claims, 3 Drawing Sheets

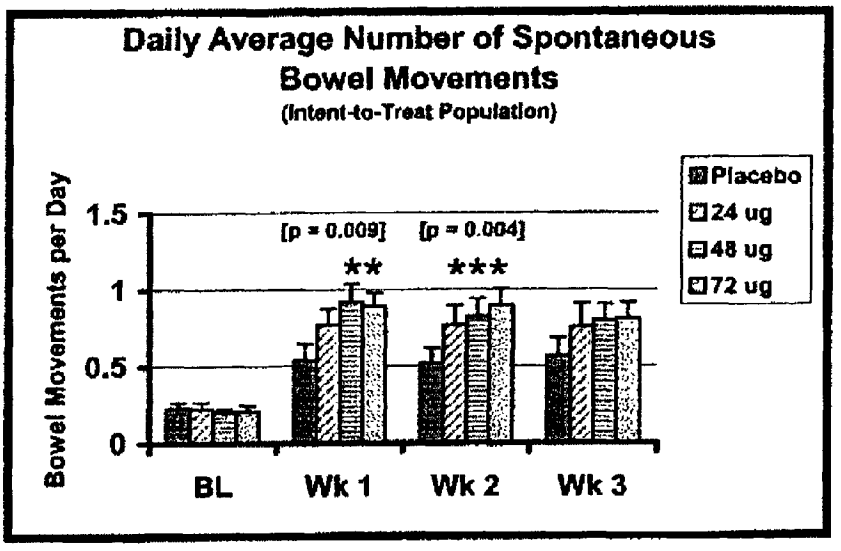

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Fig. 1

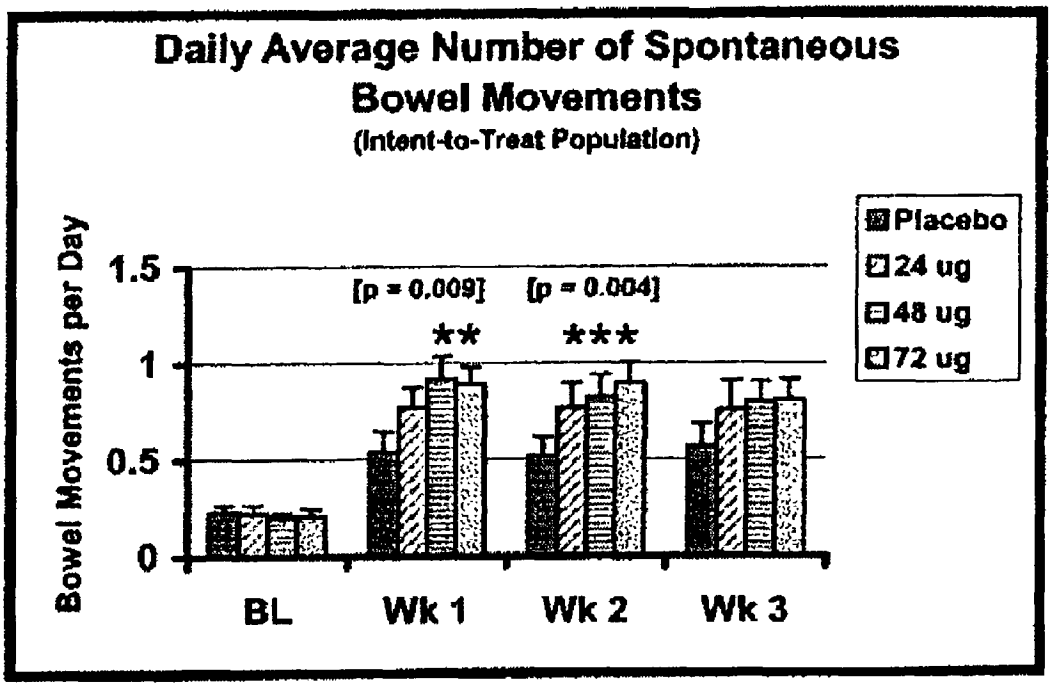

Daily Average Number of Spontaneous Bowel Movements
(Intent-to-Treat Population)
Bowel Movements per Day
1.5
1
0.5
0
[p = 0.009]
[p = 0.004]
**
***
Placebo
24 ug
48 ug
72 ug
BL
Wk 1
Wk 2
Wk 3

Fig. 2

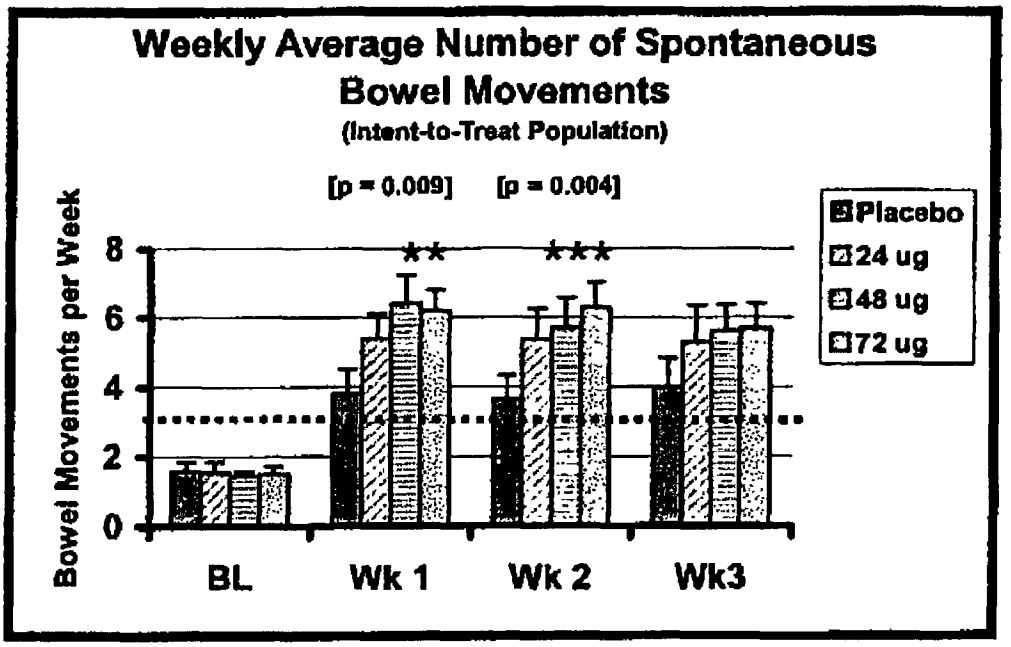
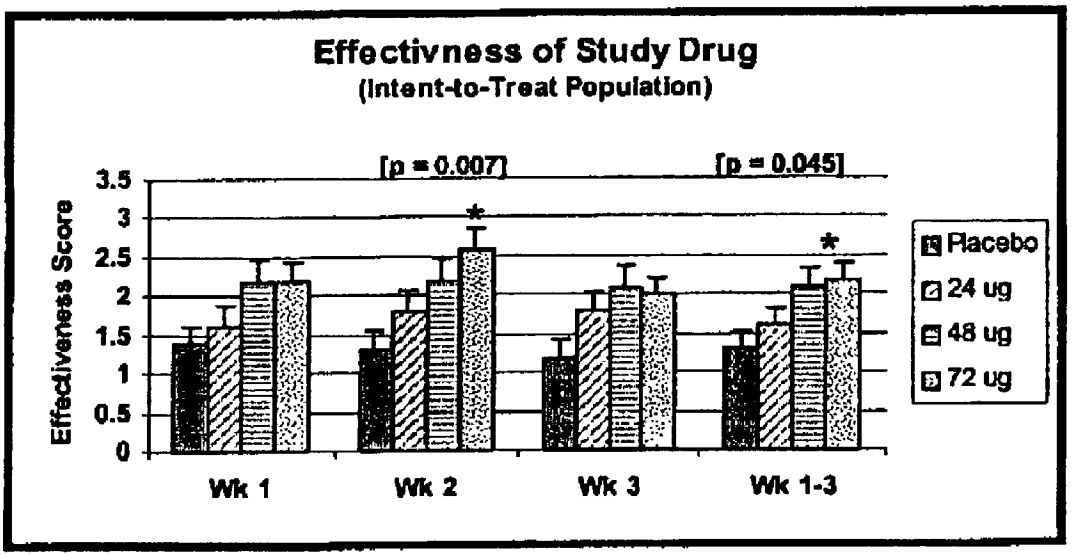

Weekly Average Number of Spontaneous Bowel Movements
(Intent-to-Treat Population)
[p = 0.009]
[p = 0.004]
Bowel Movements per Week
8
6
4
2
0
**
***
BL
Wk 1
Wk 2
Wk3
Placebo
24 ug
48 ug
72 ug

Fig. 3


Effectivness of Study Drug
(Intent-to-Treat Population)
[p = 0.007]
[p = 0.045]
Effectiveness Score
3.5
3
2.5
2
1.5
1
0.5
0
*
*
Wk 1
Wk 2
Wk 3
Wk 1-3
Placebo
24 ug
48 ug
72 ug

DOSAGE UNIT COMPRISING A PROSTAGLANDIN ANALOG FOR TREATING CONSTIPATION

This application claims benefit to Provisional Application No. 60/331,316 filed Nov. 14, 2001, the disclosure of which is incorporated herein by reference.

TECHNICAL FIELD

The present invention relates to a novel dosage unit of a halogenated prostaglandin analog for the treatment and prevention of constipation in human patients.

BACKGROUND ART

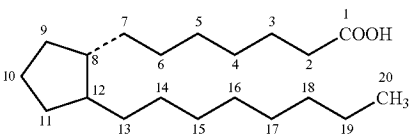
Constipation is generally defined as infrequent and difficult passage of stool. Medical reporting estimates that one of every 50 people in the United States suffers from constipation, making it one of the most common disorders among Americans. Constipation is more likely to affect females than males and more likely to occur in older adults, showing an exponential increase after the age of 65. The actual occurrence of constipation is likely higher than reported, as many individuals suffer at home without seeking professional care.

Although in some instances constipation may be caused by obstruction, most constipation can be associated with factors such as a diet low in soluble and insoluble fibers, inadequate exercise, medication use (in particular, opiate analgesics, anticholinergic antidepressants, antihistamines, and vinca alkaloids), bowel disorders, neuromuscular disorders, metabolic disorders, poor abdominal pressure or muscular atony.

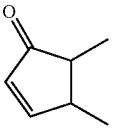
A precise quantitative definition of constipation has been difficult to establish due to the wide range of perceived "normal" bowel habits, as well as the diverse array of symptoms and signs associated with constipation. The FDA has recognized a need for prescriptive treatment of occasional constipation.

Prostaglandins (hereinafter, referred to as PGs) are members of class of organic carboxylic acids, which are contained in tissues or organs of human or other mammals, and exhibit a wide range of physiological activity. PGs found in nature (primary PGs) generally have a prostanoic acid skeleton as shown in the formula (A):

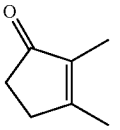
(A)



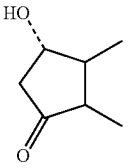
PGs are classified into several types according to the structure and substituents on the five-membered ring, for example, Prostaglandins of the A series (PGAs);



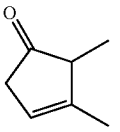
Prostaglandins of the B series (PGBs);



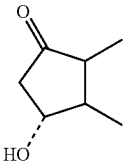
Prostaglandins of the C series (PGCs);



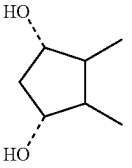
Prostaglandins of the D series (PGDs);



Prostaglandins of the E series (PGEs);



Prostaglandins of the F series (PGFs);



and the like. Further, they are classified into PG_1s containing a 13,14-double bond; PG_2s containing, 5,6- and 13,14-double bonds; and PG_3s containing 5,6-, 13,14- and 17,18-double bonds. PGs are known to have various pharmacological and physiological activities, for example, vasodilatation, inducing of inflammation, platelet aggregation, stimulating uterine muscle, stimulating intestinal muscle, anti-ulcer effect and the like. The major prostaglandins produced in the human gastrointestinal (GI) system are those of the E, I and F series (Sellin, Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management. (WB Saunders Company, 1998); Robert, Physiology of the Gastrointestinal Tract 1407-1434 (Raven, 1981); Rampton, Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids 323-344 (Churchill Livingstone, 1988); Hawkey, et al., *Gastroenterology,* 89: 1162-1188 (1985); Eberhart, et al., Gastroenterology, 109: 285-301 (1995)).

Under normal physiological conditions, endogenously produced prostaglandins play a major role in maintaining GI function, including regulation of intestinal motility and transit, and regulation of fecal consistency. (Sellin, Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management. (W B Saunders Company, 1998); Robert, Physiology of the Gastrointestinal Tract 1407-1434 (Raven, 1981); Rampton, Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids 323-344 (Churchill Livingstone, 1988); Hawkey, et al., *Gastroenterology,* 89: 1162-1188 (1985); Eberhart, et al., *Gastroenterology,* 109: 285-301 (1995); Robert, *Adv Prostaglandin Thromboxane Res,* 2:507-520 (1976); Main, et al., *Postgrad Med J,* 64 Suppl 1: 3-6 (1988); Sanders, *Am J Physiol,* 247: G117 (1984); Pairet, et al., *Am J Physiol.,* 250 (3 pt 1): G302-G308 (1986); Gaginella, Textbook of Secretory Diarrhea 15-30 (Raven Press, 1990)). When administered in pharmacological doses, both PGE_2 and $PGF_{2\alpha}$ have been shown to stimulate intestinal transit and to cause diarrhea (Robert, Physiology of the Gastrointestinal Tract 1407-1434 (Raven, 1981); Rampton, Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids 323-344 (Churchill Livingstone, 1988); Robert, *Adv Prostaglandin Thromboxane Res,* 2:507-520 (1976)). Furthermore, the most commonly reported side effect of misoprostol, a PGE_1 analogue developed for the treatment of peptic ulcer disease, is diarrhea (Monk, et al., Drugs 33 (1): 1-30 (1997)).

PGE or PGF can stimulate the intestines and cause intestinal contraction, but the enteropooling effect is poor. Accordingly, it is impossible to use PGEs or PGFs as cathartics because of side effects such as stomachache caused by the intestinal contraction.

Multiple mechanisms, including modifying enteric nerve responses, altering smooth muscle contraction, stimulating mucous secretion, stimulating cellular ionic (in particular electrogenic Cl^- transport) and increasing intestinal fluid volume have been reported to contribute to the GI effects of prostaglandins (Robert, Physiology of the Gastrointestinal Tract 1407-1434 (Raven, 1981); Rampton, Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids 323-344 (Churchill Livingstone, 1988); Hawkey, et al., *Gastroenterology,* 89: 1162-1188 (1985); Eberhart, et al., *Gastroenterology,* 109: 285-301 (1995); Robert, *Adv Prostaglandin Thromboxane Res,* 2:507-520 (1976); Main, et al., Postgrad Med J, 64 Suppl 1: 3-6 (1988); Sanders, *Am J Physiol,* 247: G117 (1984); Pairet, et al., *Am J Physiol,* 250 (3 pt 1): G302-G308 (1986); Gaginella, Textbook of Secretory Diarrhea 15-30 (Raven Press, 1990); Federal Register Vol. 50, No. 10 (GPO, 1985); Pierce, et al., *Gastroenterology* 60 (1): 22-32 (1971); Beubler, et al., *Gastroenterology,* 90: 1972 (1986); Clarke, et al., *Am J Physiol* 259: G62 (1990); Hunt, et al., *J Vet Pharmacol Ther,* 8 (2): 165-173 (1985); Dajani, et al., *Eur J Pharmacol,* 34(1): 105-113 (1975); Sellin, Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management 1451-1471 (W B Saunders Company, 1998)). Prostaglandins have additionally been shown to have cytoprotective effects (Sellin, Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management. (W B Saunders Company, 1998); Robert, *Physiology of the Gastrointestinal Tract* 1407-1434 (Raven, 1981); Robert, *Adv Prostaglandin Thromboxane Res* 2:507-520 (1976); Wallace, et al., Aiiment Pharmacol Ther 9: 227-235 (1995)).

U.S. Pat. No. 5,317,032 to Ueno et al. describes prostaglandin analog cathartics, including the existence of bicyclic tautomers and U.S. Pat. No. 6,414,016 to Ueno describes the bicyclic tautomers as having pronounced activity as anti-constipation agents. The bicyclic tautomers, substituted by

one or more halogen atoms can be employed in small doses for relieving constipation. At the C-16 position, especially, fluorine atoms, can be employed in small doses for relieving constipation. The doses, however, by which these prostaglandin analogs are optimally effective is not known. Moreover, the range at which the PG analogs are safe, while yet exerting therapeutic effects, needs to be determined. Clinical dose-ranging studies will be necessary to evaluate the safety and tolerance of PG analogs.

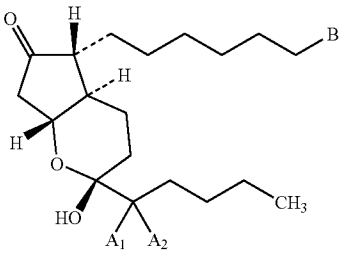
DISCLOSURE OF INVENTION

It is therefore an object of this invention to provide a dosage formulation and a workable, therapeutic approach for relieving and preventing constipation in human patients.

That is, the present invention provides a dosage unit for use in relieving or preventing constipation in a human patient comprising

(i) a prostaglandin (PG) analog represented by Formula (I) and/or its tautomer in the range of about 6-96 μg:

Formula (I)



where A_1 and A_2 are the same or different halogen atoms and

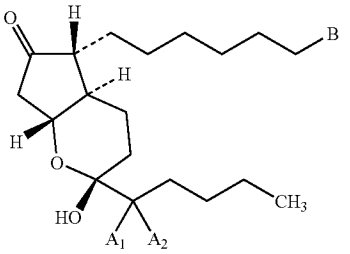
B is —COOH, including its pharmaceutically acceptable salts, esters or amides; and

(ii) a pharmaceutically suitable excipient.

Another object of the present invention is to provide a method for treating constipation in a human patient. Accordingly, the instant invention also provides a method for relieving or preventing constipation in a human patient that comprises administering to the patient a dosage unit comprising

(i) a PG analog, represented by Formula (I) and/or its tautomer in the range of about 6-96 μg:

Formula (I)



where A_1 and A_2 are the same or different halogen atoms and

B is —COOH, including its pharmaceutically acceptable salts, esters or amides; and

(ii) a pharmaceutically suitable excipient.

According to the invention, the halogenated PG analog of formula (I) is preferably halogenated with fluorine atoms, to

have a cathartic effect. The dosage unit of the invention comprises the PG analog of formula (I) and/or its tautomer in the range of about 6-96 μg per unit. A total daily dose of about 24-72 μg is also preferred. For example, the preferable total daily dose of the PG analog is about 48 μg.

According to the invention, the pharmaceutical excipient may preferably be a medium chain fatty acid to provide a dosage unit is administered orally.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1**. Graph of daily average number of spontaneous bowel movements in the intent-to-treat population. Daily bowel movements were assessed for the 0 μg, 24 μg, 48 μg and 72 μg doses of Compound A during 0, 1, 2 and 3 weeks of medicating.

In the graph, [ ]=statistically significant overall p-value based on a Cochran-Mantel Haenszel (CMH) test using modified ridit scores, controlling for site, and using Shaffer's modified sequentially rejective multiple test procedure. *=statistically significant pairwise comparison based on a Cochran-Mantel Haenszel (CMH) test comparing placebo to active drug using modified ridit scores, controlling for site and using Shaffer's modified sequentially rejective multiple test procedure.

FIG. **2**. Graph of weekly average number of spontaneous bowel movements in the intent-to-treat population. Average number of bowel movements were compared across the different treatment groups during 0 weeks, week 1, week 2 and week 3.

In the graph, [ ]=statistically significant overall p-value based on a Cochran-Mantel Haenszel (CMH) test using modified ridit scores, controlling for site, and using Shaffer's modified sequentially rejective multiple test procedure. *=statistically significant pairwise comparison based on a Cochran-Mantel Haenszel (CMH) test comparing placebo to active drug using modified ridit scores, controlling for site and using Shaffer's modified sequentially rejective multiple test procedure. Dotted line represents the cut-line for constipation defined as <3 spontaneous bowel movements per week.

FIG. **3**. Graph of study drug effectiveness in the intent-to-treat population. Effectiveness of study drug for the different treatment groups was rated on a scale of 0-4, 4 being the most effective.

In the graph, [ ]=statistically significant overall p-value based on a Cochran-Mantel Haenszel (CMH) test using modified ridit scores, controlling for site, and using Shaffer's modified sequentially rejective multiple test procedure. *=statistically significant pairwise comparison based on a Cochran-Mantel Haenszel (CMH) test comparing placebo to active drug using modified ridit scores, controlling for site and using Shaffer's modified sequentially rejective multiple test procedure. Rating scale: 0=not at all effective, 1=a little bit effective, 2=moderately effective, 3=quite a bit effective and 4=extremely effective.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a dosage unit for an anti-constipation composition comprising a halogenated prostaglandin analog as an active ingredient.

Cathartics are thought to work by the combination of one or more mechanisms to increase the water content of feces and promote transfer of the content in the intestines. Halogenated prostaglandin analogs of formula (I) appear to alleviate constipation by mainly acting on the intestinal mucosa to affect the transfer of electrolytes and water from intestinal walls into blood vessels and/or from blood vessels into intestines. These results in reduced water absorption and/or increased water secretion through intestines, increased intraintestinal water pool and transfer of the intraintestinal content.

The present inventors have discovered a dosage regimen and suitable formulations of halogenated prostaglandin analogs for the treatment and prevention of constipation. A dosage unit comprising a PG analog and a pharmaceutically suitable excipient is described herein.

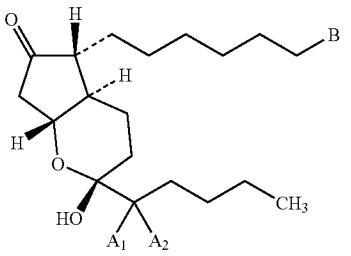
Preparing a Dosage Unit

The dosage unit comprises a prostaglandin analog of formula (I) and a pharmaceutically suitable excipient. The amount of the PG analog present in the dosage unit typically is in the range of about 6-96 μg. As used herein, the term "about" when used in conjunction with a unit of measure can be defined as +/−30% and +/−20%, preferably +/−10%. For example, the range of about 6-96 μg preferably means the range of 5.4-105.6 μg. The preferred dose is in the range of about 24-72 μg. In a more preferred embodiment, the dose is in the range of about 24-60 μg. For example, the dose of said halogenated composition can be about 48 μg. The dosage unit of the invention can be used for constipation treatment and prevention remedies for humans.

(i) PG Analogs

The PG analog, in the present invention is represented by formula (I):

Formula (I)



where A_1 and A_2 are halogen atoms and B is —COOH, its pharmaceutically acceptable salt, ester or amide.

The term "halogen" is used conventionally to include fluorine, chlorine, bromine, and iodine atoms. Particularly preferable halogen atoms for A_1 and A_2 are fluorine atoms.

The halogenated PG analog of formula (I) used in the present invention may be an amide, a salt or an ester. Such salts include pharmaceutically acceptable salts, for example, those of alkali metals such as sodium and potassium; those of alkaline earth metals such as calcium and magnesium; those of physiologically acceptable ammonium salts such as ammonia, methylamine, dimethylamine, cyclopetylamine, cylohexylamine, benzylamine, peperidine, ethylenediamine, monoethanolamine, diethanolamine, triethanolamine, monomethylmonoethanolamine, tromethamine, lysine, procaine, caffeine, arginine and tetralkylammonium salt, and the like. These salts may be prepared by a conventional process, for example, from the corresponding acid and base or by salt interchange.

Such esters include, for example, straight or branched alkyl esters, which may contain one or more unsaturated bonds such as methyl, ethyl, propyl, butyl, isopropyl, isobutyl, t-butyl, pentyl and 2-ethylhexyl.

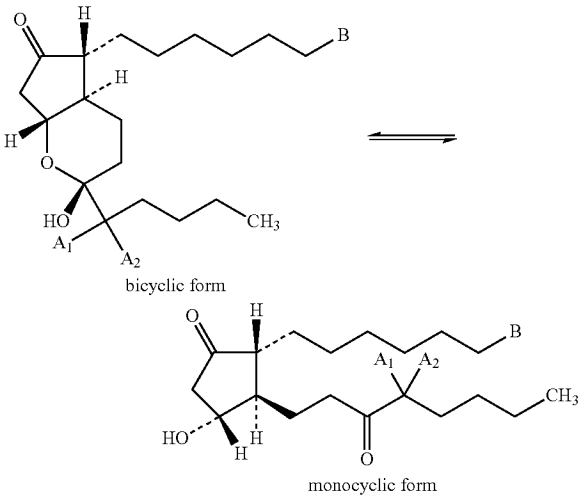
Preferred amides are methyl, ethyl, propyl, isopropyl and butyl amides.

In a preferred embodiment, the dosage unit comprises a PG analog of formula (I) in which A_1 and A_2 are fluorine atoms. Still more preferred is the one in which B is —COOH.

A dosage unit, as defined herein, is a unit of halogenated PG analog to be administered. Single or multiple dosage units may be administered, making up the dose, a quantity of halogenated PG analog that produces the desired cathartic effect.

The active agent of this invention exists as a bicyclic compound in a solid state, but partially forms a tautomer of the above compound when dissolved in a solvent. In the absence of water, compounds represented by formula (I) exist predominantly in the form of the bicyclic compound. In aqueous media, it is believed that hydrogen bonding occurs between, for example, the ketone position at the C-15 position, thereby hindering bicyclic ring formation. In addition, it is believed that the halogen atoms at the C-16 position promote bicyclic ring formation. The tautomerism between the hydroxy at the C-11 position and the keto moiety at the C-15 position, shown below, is especially significant in the case of compounds having a 13,14 single bond and two fluorine atoms the C-16 position.

Accordingly, the dosage unit of the present invention may comprise isomers of the halogenated PG analog compounds. For example, mono-cyclic tautomers having a keto group at the C-15 position and halogen atoms at the C-16 position.



A preferred compound according to the invention in its monocyclic form can be named as 13,14-dihydro-15-keto-16, 16-difluoro-PGE_1, according to conventional prostaglandin nomenclature.

(ii) The Pharmaceutically Suitable Excpient

According to the invention, the dosage unit of the invention may be formulated in any form. The pharmaceutically suitable excipient may be, therefore, selected depending on the desired form of the dosage unit. According to the invention, "pharmaceutically suitable excipient" means an inert substance, which is suitable for the form, combined with the active ingredient of the invention.

For example, solid composition for oral administration of the present invention may include tablets, preparations, granules and the like. In such a solid composition, one or more active ingredients may be mixed with at least one inactive diluent, for example, lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinyl pyrrolidone, magnesium aluminate metasilicate and the like. According to the usual work-up, the composition may contain additives other than inactive diluent, for example, lubricant such as magnesium stearate; disintegrant such as fibrous calcium gluconate; stabilizer such as cyclodextrin, for example, α,β- or γ-cyclodextrin; etherified cyclodextrin such as dimethyl-α-, dimethyl-β-, trimethyl-β-, or hydroxypropyl-β-cyclodextrin; branched cyclodextrin such as glucosyl-, maltosyl-cyclodextrin; formylated cyclodextrin, cyclodextrin containing sulfur; phospholipid and the like. When the above cyclodextrins are used, inclusion compound with cyclodextrins may be sometimes formed to enhance stability. Alternatively, phospholipid may be sometimes used to form liposome, resulting in enhanced stability.

Tablets or pills may be coated with film soluble in the stomach or intestine such as sugar, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose phthalate as needed. Further, they may be formed as capsules with absorbable substances such as gelatins. Preferably, the dosage unit is formulated in a soft gelatin capsule with liquid contents of the halogenated PG analog and a medium chain fatty acid triglyceride. Examples of the medium chain fatty acid triglyceride used in the present invention include a triglyceride of a saturated or unsaturated fatty acid having 6-14 carbon atoms which may have a branched chain. A preferred fatty acid is a straight chain saturated fatty acid, for example caproic acide (C6), caprylic acid (C8), capric acid (C10), lauric acid (C12) and myristic acid (C14). In addition, two or more medium chain fatty acid triglycerides may be used in combination. Further suitable excipients are disclosed in the published PCT application WO 01/27099.

A liquid composition for oral administration may be pharmaceutically acceptable emulsion, solution, suspension, syrup, elixir, as well as generally used inactive diluent. Such composition may contain, in addition to the inactive diluent, adjuvants such as lubricants and suspensions, sweetening agents, flavoring agents, preservatives, solubilizers, anti-oxidants and the like. The details of the additives may be selected from those described in any general textbooks in the pharmaceutical field. Such liquid compositions may be directly enclosed in soft capsules. Solutions for parenteral administration, for example, suppository, enema and the like according to the present invention include sterile, aqueous or non-aqueous solution, suspension, emulsion, detergent and the like. The aqueous solution and suspension includes, for example, distilled water, physiological saline and Ringer's solution.

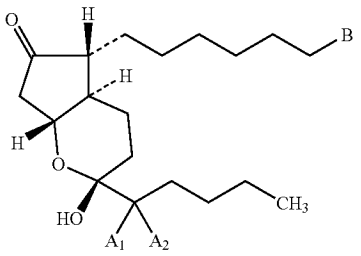
The non-aqueous solution and suspension include, for example, propylene glycol, polyethylene glycol, fatty acid triglyceride, vegetable oil such as olive oil, alcohols such as ethanol, polysorbate and the like. Such composition may contain adjuvants such as preservatives, wetting agent, emulsifier, dispersant, anti-oxidants and the like.

The dosage unit of the present invention is parenterally acceptable, however orally is preferred. The test substance is preferably dissolved in Panacet 800 (medium chain fatty acid triglyceride manufactured by Nippon Oil & Fat Co., Ltd., Amagasaki, Japan) and filled in a capsule (each capsule contains 200 μL of the mixture).

A Method for Treating Constipation

The invention further provides a method for relieving or preventing constipation in a human patient that comprises administering to the patient a dosage unit comprising (i) a PG analog represented by Formula (I) or its tautomers in the range of about 6-96 μg:

Formula I



and (ii) a pharmaceutically suitable excipient. A_1 and A_2 of the PG analog represented by Formula (I) are halogen atoms and B is —COOH, its pharmaceutically acceptable salt, ester or amide. Preferably, the halogen atoms are fluorine atoms.

According to the method of the invention, the dosage unit of the present invention can be administered systemically or locally by means of oral or parental administration, including a suppository, enema and the like. Single or multiple dosage units may be administered to achieve the desired dose.

Preferably, the total daily dose of the PG analog is in the range of about 24-72 μg. Also preferable, the total daily dose of the PG analog is in the range of about 24-60 μg. Still more preferably, the total daily dose of the PG analog is about 48 μg. The dose may vary somewhat, at the discretion of the physician, depending the age and weight of the patient, conditions, therapeutic effect, administration route, treatment time and the like.

EXAMPLES

The following examples illustrate the present invention but are not in any way intended to limit the scope of this invention. The following abbreviations are used in the examples below:

AE	Adverse Event
ITT	Intent To Treat
PO	Per Os (Orally)
PP	Per Protocol
SE	Safety Evaluable

All randomized patients who took at least one dose of double-blind study medication constituted the safety evaluable (SE) population. These patients were included in the demographic data, baseline characteristic data and safety analysis. For efficacy, the same data set was used and is referred to as the intent-to-treat (ITT) population. Patients who did not comply with the treatment regimen or who took disallowed concomitant medication were considered protocol violators. Key efficacy analyses were also performed on the per-protocol (PP) population, which excluded all data for the affected weeks for protocol violators. Patients whose treatments were adjusted were analyzed in their original treatment group (i.e., as randomized).

Example 1

Phase I Dosage Studies

The safety and tolerance of oral Compound A (13,14-dihydro-15-keto-16,16-difluoro-PGE_1) was evaluated in 16 volunteers in a single-dose Phase I study (Phase Ia) at rising per-person doses of 6 μg, 12 μg, 24 μg, 48 μg, 72 μg, and 96 μg compared and in 24 volunteers in a multiple-dose Phase I study (Phase Ib) at rising per-person doses of 24 μg, 30 μg, and 36 μg of Compound A administered three times a day (TID) (i.e., total daily per person doses of 72 μg, 90 μg and 108 μg) for 6 days.

The dose-limiting toxicity in the Phase I studies was nausea. The maximum tolerated single per-person dose of Compound A was 96 μg and the maximum tolerated multiple per-person dose of Compound A was 36 μg taken TID (i.e., a 108 μg total daily dose).

Single Rising Dose Study

96 μg was the maximum tolerated single oral Compound A dose. In the Phase Ia study, serious adverse events (SAE) did not occur at any dose level, but there were a total of 49 AEs. These occurred in 13 of the 17 volunteers and all resolved. Volunteers receiving placebo experienced five AEs. Most AEs could be categorized as either responses or events commonly reported in Phase I clinical trials (such as headache and lightheadedness) or expected pharmacodynamic responses of Compound A (such as loose bowel movements, diarrhea and abdominal cramping).

The number of adverse events increased with dose. The increase in frequency and severity of AEs found between the first four dose increments and the final two dose increments, coupled with the further increase in AEs between the final two dose increments, suggested that 96 μg was the maximum tolerated single oral Compound A dose.

Bowel movement frequency was assessed during the 24 hour period after dosing for each dose-level group. Bowel movements were experienced in the placebo and in all active dose groups. There was a trend for increased bowel movements in subjects treated with Compound A as compared to those treated with placebo. The most striking effects were seen in subjects treated at the 96 μg dose level. Compared to only three of twelve subjects experiencing bowel movements in the placebo group, all six subjects in the 96 μg Compound A group experienced bowel movements. Furthermore, the average number of bowel movements per subject in this Compound A group (1.5) was three times greater than the average number of bowel movements per subject in the placebo group (0.5).

Multiple Rising Dose Study

Compound A was determined to be optimal when administered at the 24 μg dose TID and determined to be safe and tolerable up to 36 μg when administered TID for at least 6 days. The AEs that were experienced were those that were associated with the expected pharmacologic action of Compound A. However, given that the maximal total number of bowel movements was achieved at the 24 μg dose level, and that increasing doses were not associated with increased pharmacodynamic effects, but were associated with an increased AE profile, the 24 μg dose level was determined to be the best tolerated effective dose in healthy volunteers.

The volunteers experienced no SAEs. The main dose limiting side effect observed during the study was nausea. At the 24 μg dose level, one volunteer had three bouts of nausea and at the 30 μg dose level, two volunteers experienced a total of three bouts of nausea. At the 36 μg dose level, there was a notable increase in the incidence of nausea, with thirteen bouts of nausea being experienced by five out of six volunteers dosed at this level. Further to this, one volunteer at the 36 μg level experienced twelve episodes of diarrhea or loose stools, two episodes of nausea and three episodes of abdominal cramps during the dosing period. All vital signs and ECG measurements were normal throughout the study period and no central nervous system or physical abnormalities

observed. The 36 μg dose level was determined to be the maximum tolerated multiple oral dose for the TID treatment regimen.

Bowel movement frequency was assessed in this study as well. As in the Phase I single rising dose study, the Compound A treatment groups exhibited more bowel movements than the placebo group. A total of 193 bowel movements were experienced in this study. Of these, 31 occurred in the placebo group, 70 in the 24 μg group, 51 in the 30 μg group and 41 in the 36 μg group.

Example 2

Phase II Dosage Studies

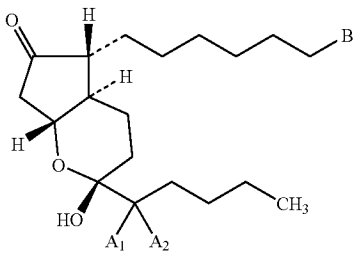
Eligible patients were treated with either placebo or total daily doses of 24 μg, 48 μg or 72 μg of Compound A for 21 days. One placebo or Compound A capsule was taken 3 times each day (AM, Noon, and PM). Compound A was administered as 24 μg oral capsules. Patients assigned to receive the total daily 24 μg Compound A dose took one Compound A capsule in the AM and one matching placebo capsule both at Noon and in the PM; patients assigned to receive the total daily 48 μg Compound A dose took one Compound A capsule in both the AM and PM and one matching placebo capsule at Noon; patients assigned to receive the total daily 72 μg Compound A dose took one Compound A capsule in the AM, at Noon, and in the PM.

Based on the overall efficacy results, doses of Compound A as low as 24 μg tended to relieve constipation, however, based on statistical analyses, the minimum effective dose of Compound A was 48 μg per day. Compared to placebo treatment, patients taking 48 μg or 72 μg of Compound A experienced statistically significant increases in the daily average number of spontaneous bowel movements at Week 1 and Week 2. Administration of 48 μg or 72 μg of Compound A produced a statistically significant increase in the proportion of patients who had a spontaneous bowel movement on Day 1. Statistically significant improvements in stool consistency were observed at all post-baseline time points in patients taking 48 μg and 72 μg of Compound A. Statistically significant improvements in constipation severity were observed at Week 3 in patients taking 48 μg of Compound A and at Weeks 2 and 3 in patients taking 72 μg of Compound A.

What is claimed is:

1. A method for relieving constipation in a human patient in need of relief of constipation that comprises administering to the patient a dosage unit comprising (i) 24 μg+/−10% of a PG analog represented by Formula (I) and/or its tautomer and (ii) a pharmaceutically suitable excipient:

Formula (I)



where A_1 and A_2 are fluorine atoms and B is —COOH, including its pharmaceutically acceptable salts, esters or amides, to thereby relieve constipation in the patient,

wherein said dosage unit is administered enough times per day so that the total daily dose of the PG analog is in the range of about 48-72 μg.

2. The method of claim **1**, wherein said PG analog is a monocyclic tautomer of formula (I).

3. The method of claim **1**, wherein said pharmaceutically suitable excipient is orally acceptable.

4. The method of claim **1**, wherein said pharmaceutically suitable excipient is a medium chain fatty acid.

5. The method of claim **1**, wherein said dosage unit is administered enough times per day so that the total daily dose of the PG analog is about 48 μg.

6. The method of claim **1**, wherein the amount of the PG analog in the dosage unit is 24 μg.

7. The method of claim **1**, wherein B is —COOH.

* * * * *

Exhibit F

US008389542B2

(12) **United States Patent**
Ueno et al.

(10) **Patent No.: US 8,389,542 B2**
(45) **Date of Patent: *Mar. 5, 2013**

(54) **DOSAGE UNIT COMPRISING A PROSTAGLANDIN ANALOG FOR TREATING CONSTIPATION**

(75) Inventors: **Ryuji Ueno**, Potomac, MD (US); **Myra L. Patchen**, Fairfax, VA (US)

(73) Assignee: **Sucampo AG**, Zug (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/330,942**

(22) Filed: **Dec. 20, 2011**

(65) **Prior Publication Data**

US 2012/0088824 A1 Apr. 12, 2012

Related U.S. Application Data

(62) Division of application No. 10/293,516, filed on Nov. 14, 2002, now Pat. No. 8,097,653.

(60) Provisional application No. 60/331,316, filed on Nov. 14, 2001.

(51) **Int. Cl.**
A61K 31/44 (2006.01)
A61K 31/34 (2006.01)
A61K 31/19 (2006.01)

(52) **U.S. Cl.** **514/302**; 514/469; 514/573

(58) **Field of Classification Search** 514/302, 514/469

See application file for complete search history.

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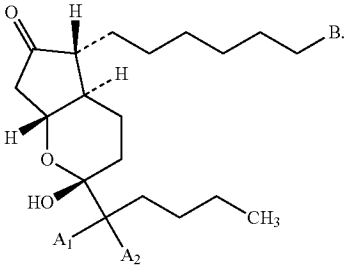
Primary Examiner — Melenie McCormick
Assistant Examiner — Gigi Huang
(74) *Attorney, Agent, or Firm* — Sughrue Mion, PLLC

(57) **ABSTRACT**

A dosage unit for treating constipation in a human patient is described. The dosage unit of the invention includes a halogenated prostaglandin analog and a pharmaceutically suitable excipient. The dosage unit relieves constipation without substantial side effects. In particular, the dosage unit includes a prostaglandin (PG) analog represented by Formula (I) and/or its tautomers, and a pharmaceutically suitable excipient, wherein the dosage unit contains the PG analog in an amount of 24 μg+/−10%:

Formula (I)



13 Claims, 3 Drawing Sheets

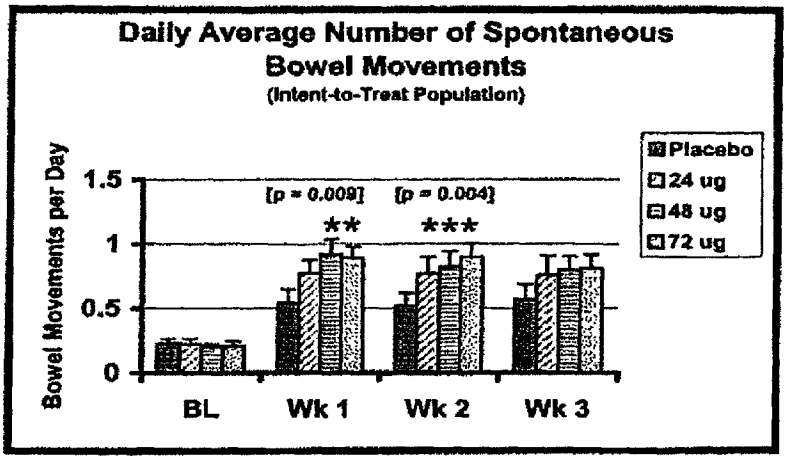


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Fig. 1

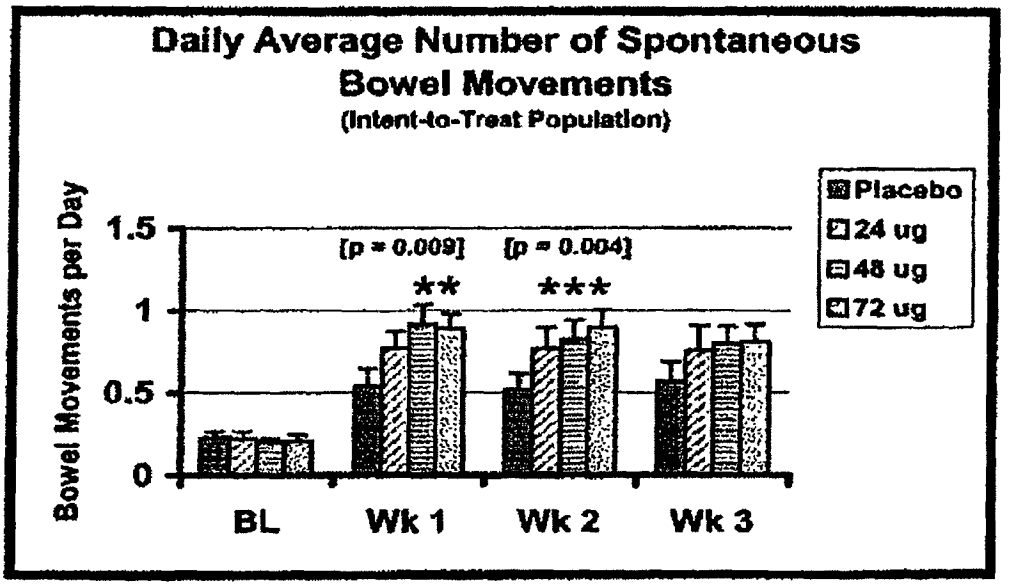

Daily Average Number of Spontaneous Bowel Movements
(Intent-to-Treat Population)
Bowel Movements per Day
1.5
1
0.5
0
[p = 0.009]
[p = 0.004]
**
***
BL
Wk 1
Wk 2
Wk 3
Placebo
24 ug
48 ug
72 ug

Fig. 2

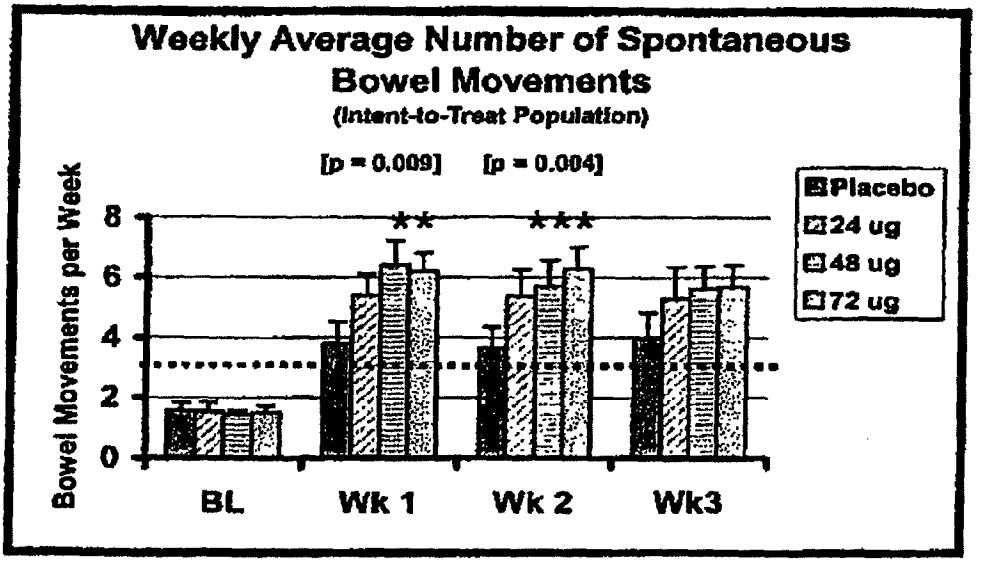
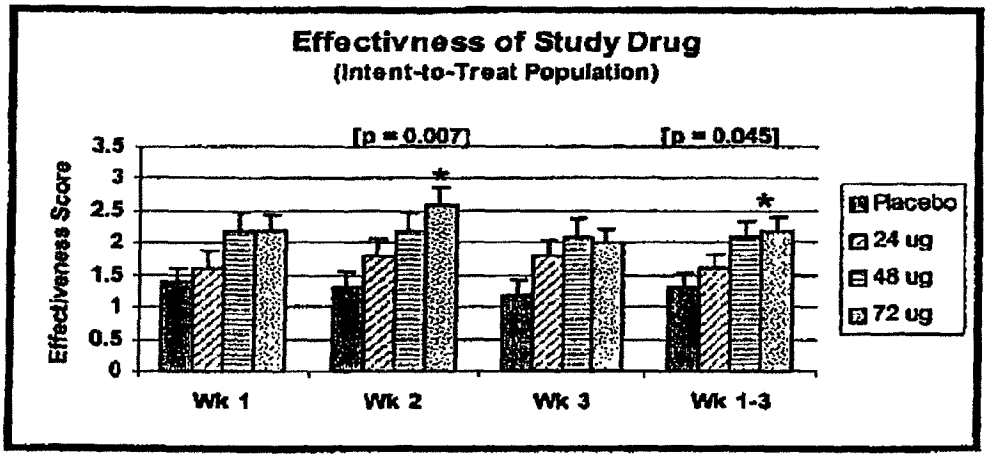

Weekly Average Number of Spontaneous Bowel Movements
(Intent-to-Treat Population)
[p = 0.009]
[p = 0.004]
Bowel Movements per Week
8
6
4
2
0
**
***
BL
Wk 1
Wk 2
Wk3
Placebo
24 ug
48 ug
72 ug

Fig. 3


Effectivness of Study Drug
(Intent-to-Treat Population)
[p = 0.007]
[p = 0.045]
Effectiveness Score
3.5
3
2.5
2
1.5
1
0.5
0
*
*
Wk 1
Wk 2
Wk 3
Wk 1-3
Placebo
24 ug
48 ug
72 ug

DOSAGE UNIT COMPRISING A PROSTAGLANDIN ANALOG FOR TREATING CONSTIPATION

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a divisional application of application Ser. No. 10/293,516 filed Nov. 14, 2002, which claims benefit to Provisional Application No. 60/331,316 filed Nov. 14, 2001, the disclosures of all of which are incorporated herein by reference.

TECHNICAL FIELD

The present invention relates to a novel dosage unit of a halogenated prostaglandin analog for the treatment and prevention of constipation in human patients.

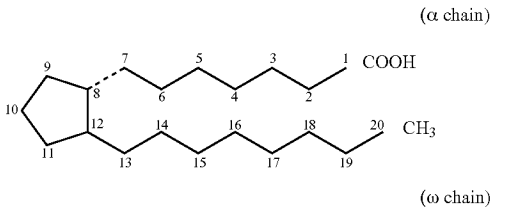
BACKGROUND ART

Constipation is generally defined as infrequent and difficult passage of stool. Medical reporting estimates that one of every 50 people in the United States suffers from constipation, making it one of the most common disorders among Americans. Constipation is more likely to affect females than males and more likely to occur in older adults, showing an exponential increase after the age of 65. The actual occurrence of constipation is likely higher than reported, as many individuals suffer at home without seeking professional care.

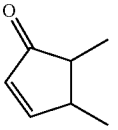
Although in some instances constipation may be caused by obstruction, most constipation can be associated with factors such as a diet low in soluble and insoluble fibers, inadequate exercise, medication use (in particular, opiate analgesics, anticholinergic antidepressants, antihistamines, and vinca alkaloids), bowel disorders, neuromuscular disorders, metabolic disorders, poor abdominal pressure or muscular atony.

A precise quantitative definition of constipation has been difficult to establish due to the wide range of perceived "normal" bowel habits, as well as the diverse array of symptoms and signs associated with constipation. The FDA has recognized a need for prescriptive treatment of occasional constipation.

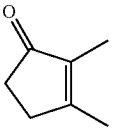
Prostaglandins (hereinafter, referred to as PGs) are members of class of organic carboxylic acids, which are contained in tissues or organs of human or other mammals, and exhibit a wide range of physiological activity. PGs found in nature (primary PGs) generally have a prostanoic acid skeleton as shown in the formula (A):



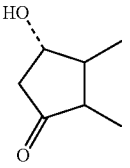
PGs are classified into several types according to the structure and substituents on the five-membered ring, for example, Prostaglandins of the A series (PGAs);



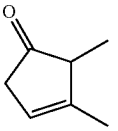
Prostaglandins of the B series (PGBs);



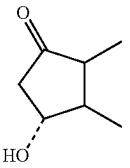
Prostaglandins of the C series (PGCs);



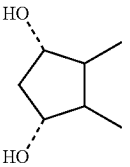
Prostaglandins of the D series (PGDs);



Prostaglandins of the E series (PGEs);



Prostaglandins of the F series (PGFs);



and the like. Further, they are classified into PG_1s containing a 13,14-double bond; PG_2s containing, 5,6- and 13,14-double bonds; and PG_3s containing 5,6-, 13,14- and 17,18-double bonds. PGs are known to have various pharmacological and physiological activities, for example, vasodilatation, inducing of inflammation, platelet aggregation, stimulating uterine

muscle, stimulating intestinal muscle, anti-ulcer effect and the like. The major prostaglandins produced in the human gastrointestinal (GI) system are those of the E, I and F series (Sellin, Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management. (WB Saunders Company, 1998); Robert, Physiology of the Gastrointestinal Tract 1407-1434 (Raven, 1981); Rampton, Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids 323-344 (Churchill Livingstone, 1988); Hawkey, et al., *Gastroenterology,* 89: 1162-1188 (1985); Eberhart, et al., *Gastroenterology,* 109: 285-301 (1995)).

Under normal physiological conditions, endogenously produced prostaglandins play a major role in maintaining GI function, including regulation of intestinal motility and transit, and regulation of fecal consistency. (Sellin, Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management. (WB Saunders Company, 1998); Robert, Physiology of the Gastrointestinal Tract 1407-1434 (Raven, 1981); Rampton, Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids 323-344 (Churchill Livingstone, 1988); Hawkey, et al., *Gastroenterology,* 89: 1162-1188 (1985); Eberhart, et al., *Gastroenterology,* 109: 285-301 (1995); Robert, *Adv Prostaglandin Thromboxane Res,* 2:507-520 (1976); Main, et al., *Postgrad Med J,* 64 Suppl 1: 3-6 (1988); Sanders, *Am J Physiol,* 247: G117 (1984); Pairet, et al., *Am J Physiol.,* 250 (3 pt 1): G302-G308 (1986); Gaginella, Textbook of Secretory Diarrhea 15-30 (Raven Press, 1990)). When administered in pharmacological doses, both PGE_2 and $PGF_{2\alpha}$ have been shown to stimulate intestinal transit and to cause diarrhea (Robert, Physiology of the Gastrointestinal Tract 1407-1434 (Raven, 1981); Rampton, Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids 323-344 (Churchill Livingstone, 1988); Robert, *Adv Prostaglandin Thromboxane Res,* 2:507-520 (1976)). Furthermore, the most commonly reported side effect of misoprostol, a PGE_1 analogue developed for the treatment of peptic ulcer disease, is diarrhea (Monk, et al., Drugs 33 (1): 1-30 (1997)).

PGE or PGF can stimulate the intestines and cause intestinal contraction, but the enteropooling effect is poor. Accordingly, it is impossible to use PGEs or PGFs as cathartics because of side effects such as stomachache caused by the intestinal contraction.

Multiple mechanisms, including modifying enteric nerve responses, altering smooth muscle contraction, stimulating mucous secretion, stimulating cellular ionic (in particular electrogenic Cl^- transport) and increasing intestinal fluid volume have been reported to contribute to the GI effects of prostaglandins (Robert, Physiology of the Gastrointestinal Tract 1407-1434 (Raven, 1981); Rampton, Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids 323-344 (Churchill Livingstone, 1988); Hawkey, et al., *Gastroenterology,* 89: 1162-1188 (1985); Eberhart, et al., Gastroenterology, 109: 285-301 (1995); Robert, *Adv Prostaglandin Thromboxane Res,* 2:507-520 (1976); Main, et al., Postgrad Med J, 64 Suppl 1: 3-6 (1988); Sanders, *Am J Physiol,* 247: G117 (1984); Pairet, et al., *Am J Physiol,* 250 (3 pt 1): G302-G308 (1986); Gaginella, Textbook of Secretory Diarrhea 15-30 (Raven Press, 1990); Federal Register Vol. 50, No. 10 (GPO, 1985); Pierce, et al., *Gastroenterology* 60 (1): 22-32 (1971); Beubler, et al., *Gastroenterology,* 90: 1972 (1986); Clarke, et al., *Am J Physiol* 259: G62 (1990); Hunt, et al., *J Vet Pharmacol Ther,* 8 (2): 165-173 (1985); Dajani, et al., *Eur J Pharmacol,* 34(1): 105-113 (1975); Sellin, Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management 1451-1471 (WB Saunders Company, 1998)). Prostaglandins have additionally been shown to have cytoprotective effects (Sellin, Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management. (WB Saunders Company, 1998); Robert, *Physiology of the Gastrointestinal Tract* 1407-1434 (Raven, 1981); Robert, *Adv Prostaglandin Thromboxane Res* 2:507-520 (1976); Wallace, et al., Aiiment Pharmacol Ther 9: 227-235 (1995)).

U.S. Pat. No. 5,317,032 to Ueno et al. describes prostaglandin analog cathartics, including the existence of bicyclic tautomers and U.S. Pat. No. 6,414,016 to Ueno describes the bicyclic tautomers as having pronounced activity as anti-constipation agents. The bicyclic tautomers, substituted by one or more halogen atoms can be employed in small doses for relieving constipation. At the C-16 position, especially, fluorine atoms, can be employed in small doses for relieving constipation. The doses, however, by which these prostaglandin analogs are optimally effective is not known. Moreover, the range at which the PG analogs are safe, while yet exerting therapeutic effects, needs to be determined. Clinical dose-ranging studies will be necessary to evaluate the safety and tolerance of PG analogs.

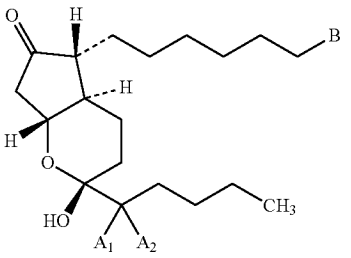
DISCLOSURE OF INVENTION

It is therefore an object of this invention to provide a dosage formulation and a workable, therapeutic approach for relieving and preventing constipation in human patients.

That is, the present invention provides a dosage unit for use in relieving or preventing constipation in a human patient comprising

(i) a prostaglandin (PG) analog represented by Formula (I) and/or its tautomer in the range of about 6-96 μg:

Formula (I)



where A_1 and A_2 are the same or different halogen atoms and

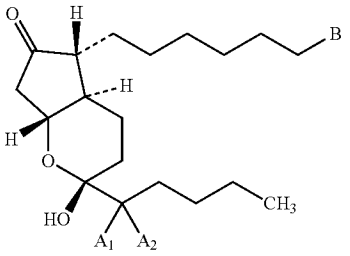
B is —COOH, including its pharmaceutically acceptable salts, esters or amides; and

(ii) a pharmaceutically suitable excipient.

Another object of the present invention is to provide a method for treating constipation in a human patient. Accordingly, the instant invention also provides a method for relieving or preventing constipation in a human patient that comprises administering to the patient a dosage unit comprising

(i) a PG analog, represented by Formula (I) and/or its tautomer in the range of about 6-96 μg:

Formula (I)



where A_1 and A_2 are the same or different halogen atoms and

B is —COOH, including its pharmaceutically acceptable salts, esters or amides; and

(ii) a pharmaceutically suitable excipient.

According to the invention, the halogenated PG analog of formula (I) is preferably halogenated with fluorine atoms, to have a cathartic effect. The dosage unit of the invention comprises the PG analog of formula (I) and/or its tautomer in the range of about 6-96 μg per unit. A total daily dose of about 24-72 μg is also preferred. For example, the preferable total daily dose of the PG analog is about 48 μg.

According to the invention, the pharmaceutical excipient may preferably be a medium chain fatty acid to provide a dosage unit is administered orally.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1**. Graph of daily average number of spontaneous bowel movements in the intent-to-treat population. Daily bowel movements were assessed for the 0 μg, 24 μg, 48 μg and 72 μg doses of Compound A during 0, 1, 2 and 3 weeks of medicating.

In the graph, [ ]=statistically significant overall p-value based on a Cochran-Mantel Haenszel (CMH) test using modified ridit scores, controlling for site, and using Shaffer's modified sequentially rejective multiple test procedure. *=statistically significant pairwise comparison based on a Cochran-Mantel Haenszel (CMH) test comparing placebo to active drug using modified ridit scores, controlling for site and using Shaffer's modified sequentially rejective multiple test procedure.

FIG. **2**. Graph of weekly average number of spontaneous bowel movements in the intent-to-treat population. Average number of bowel movements were compared across the different treatment groups during 0 weeks, week 1, week 2 and week 3.

In the graph, [ ]=statistically significant overall p-value based on a Cochran-Mantel Haenszel (CMH) test using modified ridit scores, controlling for site, and using Shaffer's modified sequentially rejective multiple test procedure. *=statistically significant pairwise comparison based on a Cochran-Mantel Haenszel (CMH) test comparing placebo to active drug using modified ridit scores, controlling for site and using Shaffer's modified sequentially rejective multiple test procedure. Dotted line represents the cut-line for constipation defined as <3 spontaneous bowel movements per week.

FIG. **3**. Graph of study drug effectiveness in the intent-to-treat population. Effectiveness of study drug for the different treatment groups was rated on a scale of 0-4, 4 being the most effective.

In the graph, [ ]=statistically significant overall p-value based on a Cochran-Mantel Haenszel (CMH) test using modified ridit scores, controlling for site, and using Shaffer's modified sequentially rejective multiple test procedure. *=statistically significant pairwise comparison based on a Cochran-Mantel Haenszel (CMH) test comparing placebo to active drug using modified ridit scores, controlling for site and using Shaffer's modified sequentially rejective multiple test procedure. Rating scale: 0=not at all effective, 1=a little bit effective, 2=moderately effective, 3=quite a bit effective and 4=extremely effective.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a dosage unit for an anti-constipation composition comprising a halogenated prostaglandin analog as an active ingredient.

Cathartics are thought to work by the combination of one or more mechanisms to increase the water content of feces and promote transfer of the content in the intestines. Halogenated prostaglandin analogs of formula (I) appear to alleviate constipation by mainly acting on the intestinal mucosa to affect the transfer of electrolytes and water from intestinal walls into blood vessels and/or from blood vessels into intestines. These results in reduced water absorption and/or increased water secretion through intestines, increased intraintestinal water pool and transfer of the intraintestinal content.

The present inventors have discovered a dosage regimen and suitable formulations of halogenated prostaglandin analogs for the treatment and prevention of constipation. A dosage unit comprising a PG analog and a pharmaceutically suitable excipient is described herein.

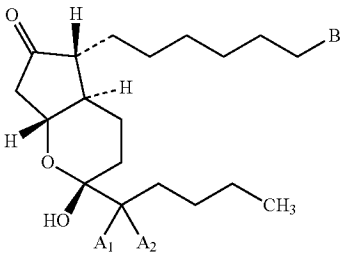
Preparing a Dosage Unit

The dosage unit comprises a prostaglandin analog of formula (I) and a pharmaceutically suitable excipient. The amount of the PG analog present in the dosage unit typically is in the range of about 6-96 μg. As used herein, the term "about" when used in conjunction with a unit of measure can be defined as +/−30% and +/−20%, preferably +/−10%. For example, the range of about 6-96 μg preferably means the range of 5.4-105.6 μg. The preferred dose is in the range of about 24-72 μg. In a more preferred embodiment, the dose is in the range of about 24-60 μg. For example, the dose of said halogenated composition can be about 48 μg. The dosage unit of the invention can be used for constipation treatment and prevention remedies for humans.

(i) PG Analogs

The PG analog, in the present invention is represented by formula (I):

Formula (I)



where A_1 and A_2 are halogen atoms and B is —COOH, its pharmaceutically acceptable salt, ester or amide.

The term "halogen" is used conventionally to include fluorine, chlorine, bromine, and iodine atoms. Particularly preferable halogen atoms for A_1 and A_2 are fluorine atoms.

The halogenated PG analog of formula (I) used in the present invention may be an amide, a salt or an ester. Such salts include pharmaceutically acceptable salts, for example, those of alkali metals such as sodium and potassium; those of alkaline earth metals such as calcium and magnesium; those of physiologically acceptable ammonium salts such as ammonia, methylamine, dimethylamine, cyclopetylamine, cylohexylamine, benzylamine, peperidine, ethylenediamine, monoethanolamine, diethanolamine, triethanolamine, monomethylmonoethanolamine, tromethamine, lysine, procaine, caffeine, arginine and tetralkylammonium salt, and the like. These salts may be prepared by a conventional process, for example, from the corresponding acid and base or by salt interchange.

Such esters include, for example, straight or branched alkyl esters, which may contain one or more unsaturated bonds such as methyl, ethyl, propyl, butyl, isopropyl, isobutyl, t-butyl, pentyl and 2-ethylhexyl.

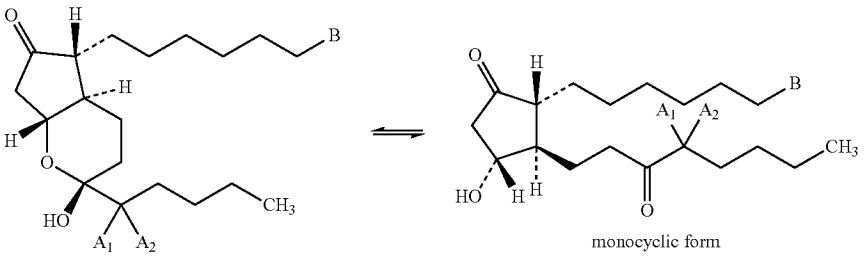
Preferred amides are methyl, ethyl, propyl, isopropyl and butyl amides.

In a preferred embodiment, the dosage unit comprises a PG analog of formula (I) in which A_1 and A_2 are fluorine atoms. Still more preferred is the one in which B is —COOH.

A dosage unit, as defined herein, is a unit of halogenated PG analog to be administered. Single or multiple dosage units may be administered, making up the dose, a quantity of halogenated PG analog that produces the desired cathartic effect.

The active agent of this invention exists as a bicyclic compound in a solid state, but partially forms a tautomer of the above compound when dissolved in a solvent. In the absence of water, compounds represented by formula (I) exist predominantly in the form of the bicyclic compound. In aqueous media, it is believed that hydrogen bonding occurs between, for example, the ketone position at the C-15 position, thereby hindering bicyclic ring formation. In addition, it is believed that the halogen atoms at the C-16 position promote bicyclic ring formation. The tautomerism between the hydroxy at the C-11 position and the keto moiety at the C-15 position, shown below, is especially significant in the case of compounds having a 13,14 single bond and two fluorine atoms the C-16 position.

Accordingly, the dosage unit of the present invention may comprise isomers of the halogenated PG analog compounds. For example, mono-cyclic tautomers having a keto group at the C-15 position and halogen atoms at the C-16 position.



bicyclic form monocyclic form

A preferred compound according to the invention in its monocyclic form can be named as 13,14-dihydro-15-keto-16, 16-difluoro-PGE_1, according to conventional prostaglandin nomenclature.

(ii) The Pharmaceutically Suitable Excipient

According to the invention, the dosage unit of the invention may be formulated in any form. The pharmaceutically suitable excipient may be, therefore, selected depending on the desired form of the dosage unit. According to the invention, "pharmaceutically suitable excipient" means an inert substance, which is suitable for the form, combined with the active ingredient of the invention.

For example, solid composition for oral administration of the present invention may include tablets, preparations, granules and the like. In such a solid composition, one or more active ingredients may be mixed with at least one inactive diluent, for example, lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinyl pyrrolidone, magnesium aluminate metasilicate and the like. According to the usual work-up, the composition may contain additives other than inactive diluent, for example, lubricant such as magnesium stearate; disintegrant such as fibrous calcium gluconate; stabilizer such as cyclodextrin, for example, α,β- or γ-cyclodextrin; etherified cyclodextrin such as dimethyl-α-, dimethyl-β-, trimethyl-β-, or hydroxypropyl-β-cyclodextrin; branched cyclodextrin such as glucosyl-, maltosyl-cyclodextrin; formylated cyclodextrin, cyclodextrin containing sulfur; phospholipid and the like. When the above cyclodextrins are used, inclusion compound with cyclodextrins may be sometimes formed to enhance stability. Alternatively, phospholipid may be sometimes used to form liposome, resulting in enhanced stability.

Tablets or pills may be coated with film soluble in the stomach or intestine such as sugar, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose phthalate as needed. Further, they may be formed as capsules with absorbable substances such as gelatins. Preferably, the dosage unit is formulated in a soft gelatin capsule with liquid contents of the halogenated PG analog and a medium chain fatty acid triglyceride. Examples of the medium chain fatty acid triglyceride used in the present invention include a triglyceride of a saturated or unsaturated fatty acid having 6-14 carbon atoms which may have a branched chain. A preferred fatty acid is a straight chain saturated fatty acid, for example caproic acide (C6), caprylic acid (C8), capric acid (C10), lauric acid (C12) and myristic acid (C14). In addition, two or more medium chain fatty acid triglycerides may be used in combination. Further suitable excipients are disclosed in the published PCT application WO 01/27099.

A liquid composition for oral administration may be pharmaceutically acceptable emulsion, solution, suspension, syrup, elixir, as well as generally used inactive diluent. Such composition may contain, in addition to the inactive diluent, adjuvants such as lubricants and suspensions, sweetening agents, flavoring agents, preservatives, solubilizers, anti-oxidants and the like. The details of the additives may be selected from those described in any general textbooks in the pharmaceutical field. Such liquid compositions may be directly enclosed in soft capsules. Solutions for parenteral adminis-

tration, for example, suppository, enema and the like according to the present invention include sterile, aqueous or non-aqueous solution, suspension, emulsion, detergent and the like. The aqueous solution and suspension includes, for example, distilled water, physiological saline and Ringer's solution.

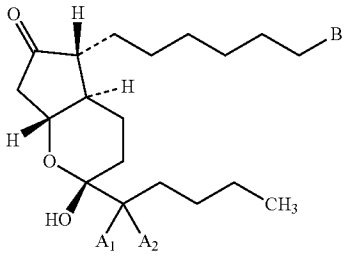
The non-aqueous solution and suspension include, for example, propylene glycol, polyethylene glycol, fatty acid triglyceride, vegetable oil such as olive oil, alcohols such as ethanol, polysorbate and the like. Such composition may contain adjuvants such as preservatives, wetting agent, emulsifier, dispersant, anti-oxidants and the like.

The dosage unit of the present invention is parenterally acceptable, however orally is preferred. The test substance is preferably dissolved in Panacet 800 (medium chain fatty acid triglyceride manufactured by Nippon Oil & Fat Co., Ltd., Amagasaki, Japan) and filled in a capsule (each capsule contains 200 μL of the mixture).

A Method for Treating Constipation

The invention further provides a method for relieving or preventing constipation in a human patient that comprises administering to the patient a dosage unit comprising (i) a PG analog represented by Formula (I) or its tautomers in the range of about 6-96 μg:

Formula I



and (ii) a pharmaceutically suitable excipient. A_1 and A_2 of the PG analog represented by Formula (I) are halogen atoms and B is —COOH, its pharmaceutically acceptable salt, ester or amide. Preferably, the halogen atoms are fluorine atoms.

According to the method of the invention, the dosage unit of the present invention can be administered systemically or locally by means of oral or parental administration, including a suppository, enema and the like. Single or multiple dosage units may be administered to achieve the desired dose.

Preferably, the total daily dose of the PG analog is in the range of about 24-72 μg. Also preferable, the total daily dose of the PG analog is in the range of about 24-60 μg. Still more preferably, the total daily dose of the PG analog is about 48 μg. The dose may vary somewhat, at the discretion of the physician, depending the age and weight of the patient, conditions, therapeutic effect, administration route, treatment time and the like.

EXAMPLES

The following examples illustrate the present invention but are not in any way intended to limit the scope of this invention. The following abbreviations are used in the examples below:

AE Adverse Event
ITT Intent To Treat
PO Per Os (Orally)
PP Per Protocol
SE Safety Evaluable

All randomized patients who took at least one dose of double-blind study medication constituted the safety evaluable (SE) population. These patients were included in the demographic data, baseline characteristic data and safety analysis. For efficacy, the same data set was used and is referred to as the intent-to-treat (ITT) population. Patients who did not comply with the treatment regimen or who took disallowed concomitant medication were considered protocol violators. Key efficacy analyses were also performed on the per-protocol (PP) population, which excluded all data for the affected weeks for protocol violators. Patients whose treatments were adjusted were analyzed in their original treatment group (i.e., as randomized).

Example 1

Phase I Dosage Studies

The safety and tolerance of oral Compound A (13,14-dihydro-15-keto-16,16-difluoro-PGE_1) was evaluated in 16 volunteers in a single-dose Phase I study (Phase Ia) at rising per-person doses of 6 μg, 12 μg, 24 μg, 48 μg, 72 μg, and 96 μg compared and in 24 volunteers in a multiple-dose Phase I study (Phase Ib) at rising per-person doses of 24 μg, 30 μg, and 36 μg of Compound A administered three times a day (TID) (i.e., total daily per person doses of 72 μg, 90 μg and 108 μg) for 6 days.

The dose-limiting toxicity in the Phase I studies was nausea. The maximum tolerated single per-person dose of Compound A was 96 μg and the maximum tolerated multiple per-person dose of Compound A was 36 μg taken TID (i.e., a 108 μg total daily dose).

Single Rising Dose Study

96 μg was the maximum tolerated single oral Compound A dose. In the Phase Ia study, serious adverse events (SAE) did not occur at any dose level, but there were a total of 49 AEs. These occurred in 13 of the 17 volunteers and all resolved. Volunteers receiving placebo experienced five AEs. Most AEs could be categorized as either responses or events commonly reported in Phase I clinical trials (such as headache and lightheadedness) or expected pharmacodynamic responses of Compound A (such as loose bowel movements, diarrhea and abdominal cramping).

The number of adverse events increased with dose. The increase in frequency and severity of AEs found between the first four dose increments and the final two dose increments, coupled with the further increase in AEs between the final two dose increments, suggested that 96 μg was the maximum tolerated single oral Compound A dose.

Bowel movement frequency was assessed during the 24 hour period after dosing for each dose-level group. Bowel movements were experienced in the placebo and in all active dose groups. There was a trend for increased bowel movements in subjects treated with Compound A as compared to those treated with placebo. The most striking effects were seen in subjects treated at the 96 μg dose level. Compared to only three of twelve subjects experiencing bowel movements in the placebo group, all six subjects in the 96 μg Compound A group experienced bowel movements. Furthermore, the average number of bowel movements per subject in this Compound A group (1.5) was three times greater than the average number of bowel movements per subject in the placebo group (0.5).

Multiple Rising Dose Study

Compound A was determined to be optimal when administered at the 24 μg dose TID and determined to be safe and tolerable up to 36 μg when administered TID for at least 6

days. The AEs that were experienced were those that were associated with the expected pharmacologic action of Compound A. However, given that the maximal total number of bowel movements was achieved at the 24 μg dose level, and that increasing doses were not associated with increased pharmacodynamic effects, but were associated with an increased AE profile, the 24 μg dose level was determined to be the best tolerated effective dose in healthy volunteers.

The volunteers experienced no SAEs. The main dose limiting side effect observed during the study was nausea. At the 24 μg dose level, one volunteer had three bouts of nausea and at the 30 μg dose level, two volunteers experienced a total of three bouts of nausea. At the 36 μg dose level, there was a notable increase in the incidence of nausea, with thirteen bouts of nausea being experienced by five out of six volunteers dosed at this level. Further to this, one volunteer at the 36 μg level experienced twelve episodes of diarrhea or loose stools, two episodes of nausea and three episodes of abdominal cramps during the dosing period. All vital signs and ECG measurements were normal throughout the study period and no central nervous system or physical abnormalities observed. The 36 μg dose level was determined to be the maximum tolerated multiple oral dose for the TID treatment regimen.

Bowel movement frequency was assessed in this study as well. As in the Phase I single rising dose study, the Compound A treatment groups exhibited more bowel movements than the placebo group. A total of 193 bowel movements were experienced in this study. Of these, 31 occurred in the placebo group, 70 in the 24 μg group, 51 in the 30 μg group and 41 in the 36 μg group.

Example 2

Phase II Dosage Studies

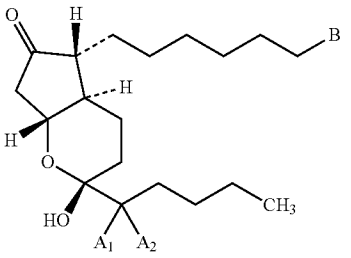
Eligible patients were treated with either placebo or total daily doses of 24 μg, 48 μg or 72 μg of Compound A for 21 days. One placebo or Compound A capsule was taken 3 times each day (AM, Noon, and PM). Compound A was administered as 24 μg oral capsules. Patients assigned to receive the total daily 24 μg Compound A dose took one Compound A capsule in the AM and one matching placebo capsule both at Noon and in the PM; patients assigned to receive the total daily 48 μg Compound A dose took one Compound A capsule in both the AM and PM and one matching placebo capsule at Noon; patients assigned to receive the total daily 72 μg Compound A dose took one Compound A capsule in the AM, at Noon, and in the PM.

Based on the overall efficacy results, doses of Compound A as low as 24 μg tended to relieve constipation, however, based on statistical analyses, the minimum effective dose of Compound A was 48 μg per day. Compared to placebo treatment, patients taking 48 μg or 72 μg of Compound A experienced statistically significant increases in the daily average number of spontaneous bowel movements at Week 1 and Week 2. Administration of 48 μg or 72 μg of Compound A produced a statistically significant increase in the proportion of patients who had a spontaneous bowel movement on Day 1. Statistically significant improvements in stool consistency were observed at all post-baseline time points in patients taking 48 μg and 72 μg of Compound A. Statistically significant improvements in constipation severity were observed at Week 3 in patients taking 48 μg of Compound A and at Weeks 2 and 3 in patients taking 72 μg of Compound A.

What is claimed is:

1. A dosage unit comprising a prostaglandin (PG) analog represented by Formula (I) and/or its tautomers, and a pharmaceutically suitable excipient, wherein the dosage unit contains said PG analog in an amount of 24 μg+/−10%:

Formula (I)



where A_1 and A_2 are fluorine atoms and

B is —COOH, including its pharmaceutically acceptable salts, esters or amides.

2. The dosage unit of claim **1**, wherein said PG analog is the monocyclic tautomer of formula (I).

3. The dosage unit of claim **1**, wherein said PG analog is the bi-cyclic tautomer of formula (I).

4. The dosage unit of claim **1**, wherein said pharmaceutically suitable excipient is orally acceptable.

5. The dosage unit of claim **1**, wherein said pharmaceutically suitable excipient is a medium chain fatty acid.

6. The dosage unit of claim **1**, wherein B is —COOH.

7. The dosage unit of claim **1**, which is suitable for use in a human patient.

8. The dosage unit of claim **7**, which is suitable for use in relieving or preventing constipation.

9. The dosage unit of claim **5**, wherein B is —COOH.

10. The dosage unit of claim **1**, wherein the PG analog is present in an amount of 24 μg.

11. The dosage unit of claim **10**, wherein B is —COOH.

12. The dosage unit of claim **10**, wherein said pharmaceutically suitable excipient is a medium chain fatty acid.

13. The dosage unit of claim **11**, wherein said pharmaceutically suitable excipient is a medium chain fatty acid.

* * * * *

Exhibit G

US008026393B2

(12) **United States Patent**
Hashitera et al.

(10) **Patent No.: US 8,026,393 B2**
(45) **Date of Patent: Sep. 27, 2011**

(54) **SOFT-GELATIN CAPSULE FORMULATION**

(75) Inventors: **Yukiko Hashitera**, Kobe (JP); **Ryu Hirata**, Sanda (JP); **Yasuhiro Harada**, Sanda (JP); **Ryuji Ueno**, Potomac, MD (US)

(73) Assignees: **Sucampo AG**, Zug (CH); **R-Tech Ueno, Ltd.**, Tokyo (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 275 days.

(21) Appl. No.: **11/656,476**

(22) Filed: **Jan. 23, 2007**

(65) **Prior Publication Data**

US 2007/0172523 A1 Jul. 26, 2007

Related U.S. Application Data

(60) Provisional application No. 60/761,360, filed on Jan. 24, 2006.

(51) **Int. Cl.**
C07C 61/06 (2006.01)
C07C 61/20 (2006.01)

(52) **U.S. Cl.** **562/504**; 514/513

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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Primary Examiner — Daniel Sullivan
Assistant Examiner — Yevegeny Valenrod
(74) *Attorney, Agent, or Firm* — Sughrue Mion, PLLC

(57) **ABSTRACT**

The present invention discloses a soft gelatin capsule formulation of a 15-keto-prostaglandin compound, which comprises: a soft gelatin capsule shell comprising gelatin and sugar alcohol as a plasticizer, and a mixture comprising a 15-keto-prostaglandin compound and a pharmaceutically acceptable vehicle which is filled in the shell. By encapsulating the 15-keto-prostaglandin compound in the specified soft gelatin capsule shell, stability of the compound is significantly improved.

22 Claims, No Drawings

SOFT-GELATIN CAPSULE FORMULATION

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. US60/761,360 filed Jan. 24, 2006.

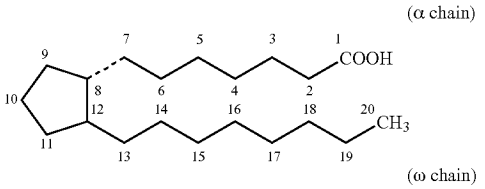
FIELD OF THE INVENTION

The present invention relates to a soft-gelatin capsule formulation of a therapeutically effective 15-keto-prostaglandin compound.

BACKGROUND ART

Prostaglandins (hereinafter, referred to as PGs) are members of class of organic carboxylic acids, which are contained in tissues or organs of human and other mammals, and exhibit a wide range of physiological activities. PGs found in nature (primary PGs) have, as a general structural property thereof, a prostanoic acid skeleton as shown in the formula (A):

(A)



On the other hand, some synthetic analogues have modified skeletons. The primary PGs are classified into PGAs, PGBs, PGCs, PGDs, PGEs, PGFs, PGGs, PGHs, PGIs and PGJs on the basis of the structural property of the five membered ring moiety, and further classified into the following three types by the number and position of the unsaturated bond in the carbon chain moiety.

Type 1 (subscript 1): 13,14-unsaturated-15-OH

Type 2 (subscript 2): 5,6- and 13,14-diunsaturated-15-OH

Type 3 (subscript 3): 5,6-, 13,14-, and 17,18-triunsaturated-15-OH.

Further, PGFs are classified on the basis of the configuration of the hydroxyl group at the 9-position into a type (wherein the hydroxyl group is of the α-configuration) and β type (wherein the hydroxyl group is of the β-configuration).

In addition, some 15-keto-PGs (PGs having an oxo group at position 15 in place of the hydroxy group) and 13,14-dihydro-15-keto-PGs have been known as substances naturally produced by enzymatic actions during metabolism of the primary PGs and have some therapeutic effect. 15-keto-PGs have been disclosed in U.S. Pat. Nos. 5,073,569, 5,534,547, 5,225,439, 5,166,174, 5,428,062 5,380,709 5,886,034 6,265,440, 5,106,869, 5,221,763, 5,591,887, 5,770,759 and 5,739,161. The contents of these publications are herein incorporated by reference.

For example, 15-keto-16-halogen prostaglandin compounds are useful as cathartics (U.S. Pat. No. 5,317,032, the contents of the reference is herein incorporated by reference). For treating gastrointestinal diseases, the agent is preferably formulated as an orally administrable dosage form. In general, PG compounds are less soluble in water and become significantly unstable under the presence of water. A capsulated formulation comprises a 15-keto-16-halogen PG compound and a solvent which can maintain the stability of the compound such as glyceride had been proposed (WO01/027099 (U.S. Pat. No. 6,583,174), the contents of the cited reference is herein incorporated by reference.

Elastic shell of a soft gelatin capsule, in general, incorporates a plasticizer in addition to gelatin. Examples of plasticizer include glycerin, propylene glycol, sorbitol, maltitol, sugar alcohol solution derived from corn starch (Anidrisorb™, Polysorb™), i.e. a mixture of sorbitol, sorbitane, mannitol and hydrogenated starch hydrolysate, hydrogenated maltose starch syrup, i.e. a mixture of maltitol, sorbitol and oligosaccharide alcohol.

SUMMARY OF THE INVENTION

An object of the present invention is to provide an orally administrable dosage form of a 15-keto-prostaglandin compound which has an excellent shelf stability.

Accordingly, the instant application provides a soft gelatin capsule formulation of a 15-keto-prostaglandin compound, which comprises:

a soft gelatin capsule shell comprising gelatin and a sugar alcohol as a plasticizer, and

a mixture comprising a 15-keto-prostaglandin compound and a pharmaceutically acceptable vehicle, which is filled in the shell.

The invention is also provides a method for improving stability of a 15-keto-prostaglandin compound which comprises, dissolving the 15-keto-prostaglandin in a pharmaceutically acceptable solvent and incorporating the solution in a soft-gelatin capsule whose shell comprises gelatin and a sugar alcohol as a plasticizer.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The nomenclature of the PG compounds used herein is based on the numbering system of prostanoic acid represented in the above formula (A).

The formula (A) shows a basic skeleton of the C-20 PG compound, but the present invention is not limited to those having the same number of carbon atoms. In the formula (A), the numbering of the carbon atoms which constitute the basic skeleton of the PG compounds starts at the carboxylic acid (numbered 1), and carbon atoms in the α-chain are numbered 2 to 7 towards the five-membered ring, those in the ring are 8 to 12, and those in the ω-chain are 13 to 20. When the number of carbon atoms is decreased in the α-chain, the number is deleted in the order starting from position 2; and when the number of carbon atoms is increased in the α-chain, compounds are named as substitution compounds having respective substituents at position 2 in place of carboxy group (C-1). Similarly, when the number of carbon atoms is decreased in the ω-chain, the number is deleted in the order starting from position 20; and when the number of carbon atoms is increased in the ω-chain, compounds are named as substitution compounds having respective substituents at position 20. Stereochemistry of the compounds is the same as that of the above formula (A) unless otherwise specified.

In general, each of PGD, PGE and PGF represents a PG compound having hydroxy groups at positions 9 and/or 11, but in the present specification and claims they also include those having substituents other than the hydroxyl groups at positions 9 and/or 11. Such compounds are referred to as 9-dehydroxy-9-substituted-PG compounds or 11-dehydroxy-11-substituted-PG compounds. A PG compound having hydrogen in place of the hydroxy group is simply named as 9- or 11-dehydroxy compound.

As stated above, the nomenclature of PG compounds is based on the prostanoic acid skeleton. However, in case the compound has a similar partial construction as a prostaglandin, the abbreviation of "PG" may be used. Thus, a PG com-

pound of which α-chain is extended by two carbon atoms, that is, having 9 carbon atoms in the α-chain is named as 2-decarboxy-2-(2-carboxyethyl)-PG compound. Similarly, a PG compound having 11 carbon atoms in the α-chain is named as 2-decarboxy-2-(4-carboxybutyl)-PG compound. Further, a PG compound of which ω-chain is extended by two carbon atoms, that is, having 10 carbon atoms in the ω-chain is named as 20-ethyl-PG compound. These compounds, however, may also be named according to the IUPAC nomenclatures.

The 15-keto-PG compound used in the present invention may be any derivative of a PG insofar as having an oxo group at position 15 in place of the hydroxy group, and may further include a compound having one double bond between positions 13 and 14 (15-keto-PG type 1 compound), two double bonds between positions 13 and 14, and positions 5 and 6 (15-keto-PG type 2 compound), and three double bonds between positions 5 and 6, positions 13 and 14, and positions 17 and 18(15-keto-PG type 3 compound), and a derivative thereof wherein the bond between the positions 13 and 14 is single bond, in place of the double bond (13,14-dihydro-15-keto-PG compound).

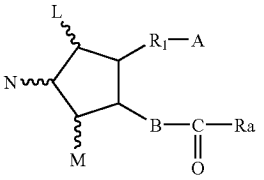
Examples of the analogue including substitution compounds or derivatives include a PG compound of which the carboxy group at the end of the alpha chain is esterified; physiologically acceptable salt thereof; an unsaturated derivative having a double bond between positions 2 and 3 or a triple bond between positions 5 and 6; PG compounds having substituent(s) on carbon atom(s) at position(s) 3, 5, 6, 16, 17, 18, 19 and/or 20; and PG compounds having lower alkyl or a hydroxy (lower) alkyl group at position 9 and/or 11 in place of the hydroxy group.

According to the present invention, preferred substituents on the carbon atom at position(s) 3, 17, 18 and/or 19 include alkyl having 1 to 6 carbon atoms, especially methyl and ethyl. Preferred substituents on the carbon atom at position 16 include lower alkyl such as methyl and ethyl, hydroxy, halogen atom such as chlorine and fluorine, and aryloxy such as trifluoromethylphenoxy. Preferred substituents on the carbon atom at position 17 include halogen atom such as chlorine and fluorine. Preferred substituents on the carbon atom at position 20 include saturated or unsaturated lower alkyl such as C_{1-4} alkyl, lower alkoxy such as C_{1-4} alkoxy, and lower alkoxy alkyl such as C_{1-4} alkoxy-C_{1-4} alkyl. Preferred substituents on the carbon atom at position 5 include halogen atoms such as chlorine and fluorine. Preferred substituents on the carbon atom at position 6 include an oxo group forming a carbonyl group. Stereochemistry of PGs having hydroxy, lower alkyl or hydroxy(lower)alkyl substituent on the carbon atom at positions 9 and 11 may be α, β or a mixture thereof.

Further, the above described derivatives may have a ω chain shorter than that of the primary PGs and a substituent such as alkoxy, cyclohexyl, cyclohexyloxy, phenoxy and phenyl at the end of the truncated ω-chain.

Especially preferred compounds include a 13,14-dihydro-15-keto-PG compound that has a single bond between positions 13 and 14; a 15-keto-16-mono or 16,16-di-halogen PG compound that has at least one halogen atom, especially fluorine, at carbon atom of position 16; a 15-keto-PGE compound that has hydroxy group at position 9 and oxo group at position 11 of the five membered ring.

A preferred prostaglandin compound used in the is present invention is represented by the formula (I):



(I)

wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

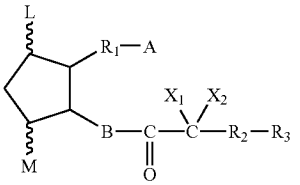
A is —CH_3, or —CH_2OH, —$COCH_2OH$, —COOH or a functional derivative thereof;

B is —CH_2—CH_2—, —CH═CH— or —C≡C—;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

Ra is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclicoxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower) alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclicoxy group.

A more preferred prostaglandin compound used in the present invention is represented by the formula (II):



(II)

wherein L and M are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have one or more double bonds;

A is —CH_3, or —CH_2OH, —$COCH_2OH$, —COOH or a functional derivative thereof;

B is —CH_2—CH_2—, —CH═CH— or —C≡C—;

X_1 and X_2 are hydrogen, lower alkyl, or halogen;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur;

R_2 is a single bond or lower alkylene; and

R_3 is lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo (lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclicoxy group.

In the above formula, the term "unsaturated" in the definitions for R_1 and Ra is intended to include at least one or more double bonds and/or triple bonds that are isolatedly, separately or serially present between carbon atoms of the main and/or side chains. According to the usual nomenclature, an

unsaturated bond between two serial positions is represented by denoting the lower number of the two positions, and an unsaturated bond between two distal positions is represented by denoting both of the positions.

The term "lower or medium aliphatic hydrocarbon" refers to a straight or branched chain hydrocarbon group having 1 to 14 carbon atoms (for a side chain, 1 to 3 carbon atoms are preferable) and preferably 1 to 10, especially 6 to 10 carbon atoms for R_1 and 1 to 10, especially, 1 to 8 carbon atoms for Ra.

The term "halogen" covers fluorine, chlorine, bromine and iodine.

The term "lower" is intended to include a group having 1 to 6 carbon atoms unless otherwise specified.

The term "lower alkyl" refers to a straight or branched chain saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl and hexyl.

The term "lower alkoxy" refers to a group of lower alkyl-O—, wherein lower alkyl is as defined above.

The term "hydroxy(lower)alkyl" refers to a lower alkyl as defined above which is substituted with at least one hydroxy group such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 1-methyl-1-hydroxyethyl.

The term "lower alkanoyloxy" refers to a group represented by the formula RCO—O—, wherein RCO— is an acyl group formed by oxidation of a lower alkyl group as defined above, such as acetyl.

The term "cyclo(lower)alkyl" refers to a cyclic group formed by cyclization of a lower alkyl group as defined above but contains three or more carbon atoms, and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cyclo(lower)alkyloxy" refers to the group of cyclo(lower)alkyl-O—, wherein cyclo(lower)alkyl is as defined above.

The term "aryl" may include unsubstituted or substituted aromatic hydrocarbon rings (preferably monocyclic groups), for example, phenyl, tolyl, xylyl. Examples of the substituents are halogen atom and halo(lower)alkyl, wherein halogen atom and lower alkyl are as defined above.

The term "aryloxy" refers to a group represented by the formula ArO—, wherein Ar is aryl as defined above.

The term "heterocyclic group" may include mono- to tricyclic, preferably monocyclic heterocyclic group which is 5 to 14, preferably 5 to 10 membered ring having optionally substituted carbon atom and 1 to 4, preferably 1 to 3 of 1 or 2 type of hetero atoms selected from nitrogen, oxygen and sulfur. Examples of the heterocyclic group include furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, 2-pyrrolinyl, pyrrolidinyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, piperidino, piperazinyl, morpholino, indolyl, benzothienyl, quinolyl, isoquinolyl, purinyl, quinazolinyl, carbazolyl, acridinyl, phenanthridinyl, benzimidazolyl, benzimidazolinyl, benzothiazolyl, phenothiazinyl. Examples of the substituent in this case include halogen, and halogen substituted lower alkyl group, wherein halogen atom and lower alkyl group are as described above.

The term "heterocyclicoxy group" means a group represented by the formula HcO—, wherein Hc is a heterocyclic group as described above.

The term "functional derivative" of A includes salts, preferably pharmaceutically acceptable salts, ethers, esters and amides.

Suitable "pharmaceutically acceptable salts" include salts formed with non-toxic bases conventionally used in pharmaceutical field, for example a salt with an inorganic base such as an alkali metal salt (such as sodium salt and potassium salt), an alkaline earth metal salt (such as calcium salt and magnesium salt), an ammonium salt; or a salt with an organic base, for example, an amine salt including such as methylamine salt, dimethylamine salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, tris (hydroxymethylamino)ethane salt, monomethylmonoethanolamine salt, procaine salt and caffeine salt), a basic amino acid salt (such as arginine salt and lysine salt), tetraalkyl ammonium salt and the like. These salts may be prepared by a conventional process, for example from the corresponding acid and base or by salt interchange.

Examples of the ethers include alkyl ethers, for example, lower alkyl ethers such as methyl ether, ethyl ether, propyl ether, isopropyl ether, butyl ether, isobutyl ether, t-butyl ether, pentyl ether and 1-cyclopropyl ethyl ether; and medium or higher alkyl ethers such as octyl ether, diethylhexyl ether, lauryl ether and cetyl ether; unsaturated ethers such as oleyl ether and linolenyl ether; lower alkenyl ethers such as vinyl ether, allyl ether; lower alkynyl ethers such as ethynyl ether and propynyl ether; hydroxy(lower)alkyl ethers such as hydroxyethyl ether and hydroxyisopropyl ether; lower alkoxy (lower)alkyl ethers such as methoxymethyl ether and 1-methoxyethyl ether; optionally substituted aryl ethers such as phenyl ether, tosyl ether, t-butylphenyl ether, salicyl ether, 3,4-di-methoxyphenyl ether and benzamidophenyl ether; and aryl(lower)alkyl ethers such as benzyl ether, trityl ether and benzhydryl ether.

Examples of the esters include aliphatic esters, for example, lower alkyl esters such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester and 1-cyclopropylethyl ester; lower alkenyl esters such as vinyl ester and allyl ester; lower alkynyl esters such as ethynyl ester and propynyl ester; hydroxy(lower) alkyl ester such as hydroxyethyl ester; lower alkoxy (lower) alkyl esters such as methoxymethyl ester and 1-methoxyethyl ester; and optionally substituted aryl esters such as, for example, phenyl ester, tolyl ester, t-butylphenyl ester, salicyl ester, 3,4-di-methoxyphenyl ester and benzamidophenyl ester; and aryl(lower)alkyl ester such as benzyl ester, trityl ester and benzhydryl ester.

The amide of A means a group represented by the formula —CONR'R", wherein each of R' and R" is hydrogen, lower alkyl, aryl, alkyl- or aryl-sulfonyl, lower alkenyl and lower alkynyl, and include for example lower alkyl amides such as methylamide, ethylamide, dimethylamide and diethylamide; arylamides such as anilide and toluidide; and alkyl- or arylsulfonylamides such as methylsulfonylamide, ethylsulfonylamide and tolylsulfonylamide.

Preferred examples of L and M include hydroxy and oxo, and especially, M is hydroxy and L is oxo which has a 5-membered ring structure of, so called, PGE type.

Preferred example of A is —COOH, its pharmaceutically acceptable salt, ester or amide thereof.

Preferred example of B is $—CH_2—CH_2—$, which provide the structure of so-called, 13,14-dihydro type.

Preferred example of X_1 and X_2 is that at least one of them is halogen, more preferably, both of them are halogen, especially, fluorine that provides a structure of, so called 16,16-difluoro type.

Preferred R_1 is a hydrocarbon residue containing 1-10 carbon atoms, preferably 6 to 10 carbon atoms. Further, at least one carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur.

Examples of R_1 include, for example, the following groups:

$—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—$,
$—CH_2—CH=CH—CH_2—CH_2—CH_2—$,
$—CH_2—CH_2—CH_2—CH_2—CH=CH—$,
$—CH_2—C\equiv C—CH_2—CH_2—CH_2—$,
$—CH_2—CH_2—CH_2—CH_2—CH(CH_3)—CH_2—$,
$—CH_2—CH_2—CH_2—CH_2—O—CH_2—$,
$—CH_2—CH=CH—CH_2—O—CH_2—$,
$—CH_2—C\equiv C—CH_2—O—CH_2—$,
$—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—$,
$—CH_2—CH=CH—CH_2—CH_2—CH_2—CH_2—$,

—CH_2—CH_2—CH_2—CH_2—CH_2—CH═CH—,
—CH_2—C≡C—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—$CH(CH_3)$—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH═CH—CH_2—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2CH_2—CH═CH—,
—CH_2—C═C—CH_2—CH_2—CH_2—CH_2—CH_2—, and
—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—$CH(CH_3)$—CH_2—.

Preferred Ra is a hydrocarbon containing 1 to 10 carbon atoms, more preferably, 1 to 8 carbon atoms. Ra may have one or two side chains having one carbon atom.

The configuration of the ring and the α- and/or ω chains in the above formula (I) and (II) may be the same as or different from that of the primary PGs. However, the present invention also includes a mixture of a compound having a primary type configuration and a compound of a non-primary type configuration.

The typical example of the present compounds are 13,14-dihydro-15-keto-16-mono- or 16,16-di-fluoro PGE compound and its derivative or analogue.

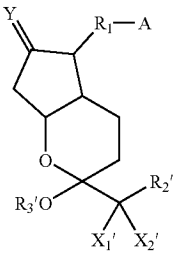
In the present invention, the 15-keto-PG compound may be in the keto-acetal equilibrium by formation of a hemiacetal between hydroxy at position 11 and keto at position 15.

For example, it has been revealed that when both of X_1 and X_2 are halogen atoms, especially, fluorine atoms, the compound contains a tautomeric isomer, bi-cyclic compound.

If such tautomeric isomers as above are present, the proportion of both tautomeric isomers varies with the structure of the rest of the molecule or the kind of the substituent present. Sometimes one isomer may predominantly be present in comparison with the other. However, it is to be appreciated that the present invention includes both isomers.

Further, the 15-keto-PG compounds used in the invention include the bi-cyclic compound and analogs or derivatives thereof.

The bi-cyclic compound is represented by the formula (III):



(III)

wherein, A is —CH_3, or —CH_2OH, —$COCH_2OH$, —COOH or a functional derivative thereof;

X_1' and X_2' are hydrogen, lower alkyl, or halogen;

Y is

wherein R_4' and R_5' are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R_4' and R_5' are not hydroxy and lower alkoxy at the same time;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur;

R_2' is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclicoxy group; lower alkyl; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclicoxy group; and

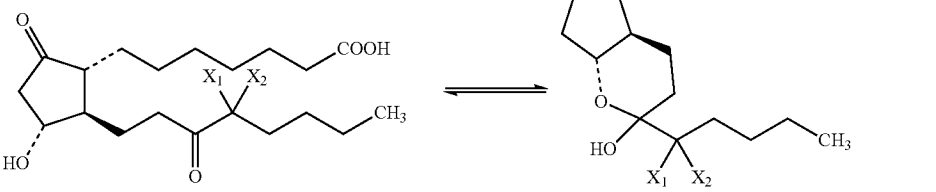
R_3' is hydrogen, lower alkyl, cyclo(lower)alkyl, aryl or heterocyclic group.

Furthermore, while the compounds used in the invention may be represented by a formula or name based on keto-type regardless of the presence or absence of the isomers, it is to be noted that such structure or name does not intend to exclude the acetal type compound.

In the present invention, any of isomers such as the individual tautomeric isomers, the mixture thereof, or optical isomers, the mixture thereof, a racemic mixture, and other steric isomers may be used in the same purpose.

Some of the compounds used in the present invention may be prepared by the method disclosed in U.S. Pat. Nos. 5,073,569, 5,166,174, 5,221,763, 5,212,324, 5,739,161 and 6,242,485, the contents of these references are herein incorporated by reference.

It has been known that 13,14-dihydro-15-keto-prostaglandin compound having the formula as shown below (Tautomer I) may be in equilibrium with its tautomeric isomer (tautomer II) (See U.S. Pat. No. 5,166,174, U.S. Pat. No. 5,225,439, U.S. Pat. No. 5,284,858, U.S. Pat. No. 5,380,709, U.S. Pat. No. 5,428,062 and U.S. Pat. No. 5,886,034, the contents of these references are herein incorporated by reference.)

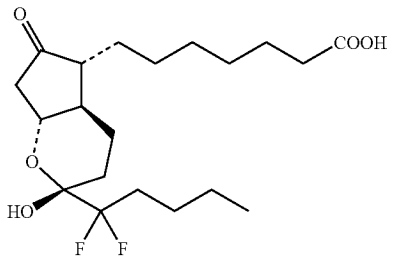


Tautomer I Tautomer II

It is considered that the halogen atom(s) at X_1 and/or X_2 promote bi-cyclic ring formation, such as the compound 1 or 2 below. In addition, in the absence of water, the tautomeric compounds as above exist predominantly in the form of the bi-cyclic compound. In aqueous media, it is supposed that hydrogen bonding occurs between the water molecule and, for example, the keto group on the hydrocarbon chain, thereby hindering bi-cyclic ring formation. The bi-cyclic/mono-cyclic structures, for example, may be present in a ratio of 6:1 in D_2O; 10:1 in CD_3OD-D_2O and 96:4 in $CDCl_3$. In the instant specification and claims, tautomeric mixture containing the bi-cyclic compound in a ratio even greater to substantially 100% bi-cyclic compound is within this invention.

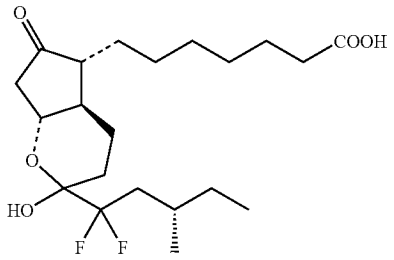
Embodiment of the bi-cyclic compound of the present invention include the Compounds 1 and 2 shown below.

Compound 1:



7-[(2R,4aR,5R,7aR)-2-(1,1-difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[b]pyran-5-yl]heptanoic acid

Compound 2:



7-{(4aR,5R,7aR)-2-[(3S)-1,1-difluoro-3-methylpentyl]-2-hydroxy-6-oxooctahydrocyclopenta[b]pyran-5-yl}heptanoic acid

According to the present invention, the pharmaceutically acceptable vehicle is not specifically limited as long as the vehicle can disperse the 15-keto-PG therein and does not significantly deteriorate the stability of the compound. In view of manufacturing soft gelatin capsule formulation, a solvent which is liquid at the room temperature. A solution, dispersion or mixture of the 15-keto-PG in the solvent may be filled in the capsule.

Examples of the pharmaceutically acceptable vehicles preferably used in the instant invention may be fatty acid esters, i.e. an ester of fatty acid and an alcohol, and polyols.

Preferred fatty acid which consists the fatty acid ester is a medium or higher chain fatty acid having at least C6, preferably C6-24 carbon atoms, for example caproic acid (C6), caprylic acid (C8), capric acid (C10), lauric acid (C12) and myristic acid (C14), palmitic acid (C16), palmitoleic acid (C16), stearic acid (C18), oleic acid (C18), linoleic acid (C18), linolenic acid (C18), ricinolic acid (C18) and arachic acid (C20). Preferred alcohols which consists the fatty acid ester may comprise C1-6 monovalent alcohol and polyols such as glycerin, polyethylene glycol and propylene glycol.

Preferred fatty acid esters may include a glyceride of a saturated or unsaturated fatty acid which may have a branched chain and a propylene glycol fatty acid ester. Two or more glycerides may be used as a mixture.

Examples of the mixture of glycerides are mixture of caprylic acid triglyceride and capric acid triglyceride, vegetable oils such as castor oil, corn oil, olive oil, sesame oil, rape oil, salad oil, cottonseed oil, camellia oil, peanut oil, palm oil and sunflower oil.

A fatty acid ester derived from a fatty acid and a monovalent alcohol is also preferably used as a pharmaceutically acceptable vehicle. The fatty acid ester may preferably be an ester of C8-20 fatty acid and a C2-3 monovalent alcohol, such as isopropyl myristate, isopropyl palmitate, ethyl linoleate and ethyl oleate.

Examples of polyols may preferably include alcohols having two or three hydroxy groups such as glycerin, polyethylene glycol and propylene glycol.

According to the present invention, the mixture which is filled in the soft-gelatin capsule shell may be obtained by dissolving or dispersing the above-described 15-keto-prostaglandin compound in the above described pharmaceutically acceptable vehicle which is liquid at the room temperature. When it is difficult to dissolve the 15-keto-PG compound directly in the vehicle, each of them may be dissolved in a solvent in which both of them are soluble respectively, and then the solutions may be combined.

The amount of the solvent in the mixture relative to the amount of the 15-keto-PG compound is not limited as long as the 15-keto-PG is stable in the final formulation. In general, the amount of the vehicle per one part of the 15-keto-PG compound may be 1-5,000,000, preferably, 5-1,000,000 and most preferably, 10-500,000 parts by weight.

The mixture used in the invention may further comprise an oil solvent such as mineral oil, liquid paraffin, and tocopherol. The mixture of the present invention may further comprise another pharmaceutically active ingredient.

In a preferred embodiment, the composition of the present invention is substantially free of water. The term "substantially free of water" means that the composition does not contain water that is intentionally added. It is understood that many materials contain water that is taken up from the atmosphere or is present as a coordination complex in its normal state. Water taken up by hygroscopic materials or present as a hydrate is permissibly present in the compositions of this embodiment. According to the embodiment, any water that is present in the composition should not be present in amounts such that the water will have a deleterious effect to the composition of the present invention.

According to the present invention, the shell of the soft gelatin capsule is manufactured from gelatin and a sugar alcohol as a plasticizer.

Sugar alcohol used in the present invention is an alcohol obtained by hydrogen reduction of the aldehyde group of a saccharide. For example, sorbitol, mannitol, maltitol, lactitol, palatinit, xylitol, erithyritol, sugar alcohol solution derived from corn starch, i.e. a mixture of sorbitol, sorbitan, mannitol

and hydrogenated starch hydrolysate, hydrogenated maltose starch syrup, i.e. a mixture of maltitol, sorbitol and oligosaccharide alcohol. Preferred sugar alcohols may include sorbitol, maltitol, sugar alcohol solution derived from corn starch and hydrogenated maltose starch syrup. Especially, sugar alcohol solution derived from corn starch and available on market under the name "Anidrisorb™" or "Polysorb™" is preferably used.

According to the invention, the amount of the sugar alcohol used for preparing the shell of the soft gelatin capsule is not specifically limited as long as the physical properties of the resulting capsule is not deteriorated. In general, the amount of sugar alcohol plasticizer is 20 to 60 parts by weight, preferably, 30 to 50 parts by weight per 100 parts by weight of gelatin.

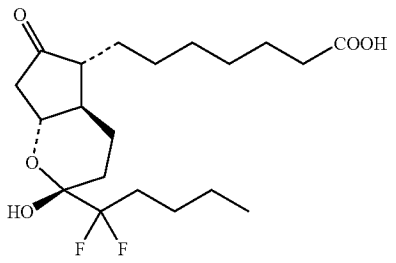
The soft gelatin capsule formulation of the 15-keto-PG compound may be manufactured according to a conventional manner using the above described liquid mixture and a mixture of gelatin and the plasticizer.

The present invention will be explained in more detail by means of the following examples, which are illustrated by way of example only and never intended to limit the scope of the present invention.

Reference Example 1

Compound 1 was dissolved in a vehicle shown in table 1 below to give 240 μg/g solution (sample). The precise concentration of compound 1 in the sample was determined by means of HPLC (day 0). Then, the sample was put in a hard grass container and kept at 55° C. for 10 days, and then the precise concentration of the compound 1 in the sample was determined by means of HPLC (day 10).

Compound 1



The determination of the concentration of the compound in the sample was carried out as follows. About 0.2 g of the sample was mixed with exactly 2 ml of internal standard solution and then with a dissolving agent shown in Table 1 to give 5 mL of sample solution. About 12 mg of the reference standard compound 1 was weighted precisely and added with acetonitrile to give exactly 100 ml solution. Exactly 0.8 ml of the solution was obtained and added with exactly 4 ml of the internal standard solution, and then added with the dissolving agent to give 10 ml of standard solution.

The fluorescent labeling agent was added to the respective solution, stirred and stood at room temperature. Then, respective solution in an amount that theoretically gives 3-6 ng of compound 1 was loaded on the column and analyzed under the condition as follows:

HPLC Analysis Condition:

Column; 5 mm×25 cm stainless steel column packed with octadecylsilane treated silica gel for HPLC (5 μm)

Mobile phase: mixture of acetonitrile HPLC grade: methanol HPLC grade: ammonium acetate (0.05 mol/L)

Temperature: 35° C.

Detector: spectrophotofluorometer

Results are shown in Table 1:

TABLE 1

Assay results of compound 1 after 55° C. storage

	vehicle	dissolving agent	concentration of compound 1[1] day 0	concentration of compound 1[1] day 10
1	hydrogenated maltose starch syrup	acetonitrile/ Water (1:1)	—	24.4%
2	Sugar alcohol solution derived from corn starch[2]	methanol	—	26.2%
3	glycerin	methanol	92.0%	78.0%
4	propylene glycol	acetonitrile	97.8%	88.6%
5	polyethylene glycol 400	acetonitrile	98.2%	90.1%

[1]Percentage based on a theoretical amount (240 μg/g)

[2]Polysorb 85/70/00 ™, ROQUETTE AMERICA, Inc.

Example 1

One hundred (100) parts by weight of gelatin (type A, high bloom, SKW Biosystems #195F) and 35 parts by weight of a plasticizer shown in Table 2 were mixed in water and dried to give gelatin piece. Compound 1 was dissolved in medium chain fatty acid triglyceride (USP/NF grade) to give a liquid mixture comprising 60 μg/g of the compound. 0.5 g of the liquid mixture and 0.5 g of each gelatin piece were put together in a sealed container and kept at 40° C. for 21 days. Then, the concentration of compound 1 contained in the liquid mixture was determined in the same manner as Reference Example 1. Results are shown in Table 2:

TABLE 2

Stability data of compound 1/medium chain fatty acid triglyceride (MCT) solution (60 μg/g)

gelatin piece: plasticizer	gelatin piece: water content (after dried)	concentration of compound 1: after storage[1]
glycerin	23%	86.8%
sugar alcohol solution derived from corn starch[2]	25%	92.0%

[1]Percentage based on a theoretical amount (60 μg/g)

[2]Polysorb 85/70/00 ™, ROQUETTE AMERICA, Inc.

According to the reference example 1, in case the 15-keto-prostaglandin compound of the invention and the sugar alcohol were contacted directly, stability of the compound was significantly lowered. In contrast, in case the 15-keto-PG compound was directly contacted with a polyol such as glycerin, the stability of the compound was maintained. It have surprisingly revealed by Example 1 that the stability of the 15-keto-prostaglandin contacted with gelatin piece prepared using sugar alcohol as a plasticizer was better than that contacted with gelatin piece with glycerin as a plasticizer.

Example 2

Sugar alcohol solution derived from corn starch in an amount shown in Table 3 was added in an appropriate amount

of water, stirred and heated. Then, gelatin 100 parts by weight was added thereto to give gelatin solution. Compound 1 was dissolved in medium chain fatty acid triglyceride (USP/NF grade) to give a fill solution containing 240 μg/g of compound 1. The gelatin solution and the liquid mixture were loaded or capsule forming and filling machine to give capsule containing the fill solution therein, and the capsule was dried to give soft gelatin capsule.

The capsule was put in a sealed container and kept at 40° C. for 3 months. The concentration of compound 1 in the fill solution contained in the capsule was determined after 1, 2 and 3 months storage in the same manner as Reference Example 1.

TABLE 3

Stability of soft gelatin capsule of compound 1

soft gelatin capsule (parts by weight)				conc. (% of Initial) 40° C. 1 mo	2 mo	3 mo
gelatin	100	sugar	35	99.9%	100.3%	99.2%
		alcohol	45	—	100.5%	100.0%
		solution[1)]	55	—	99.3%	100.0%

[1)]Polysorb 85/70/00 ™, ROQUETTE AMERICA, Inc., derived from corn starch

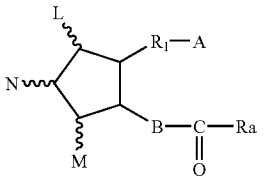
What is claimed is:

1. A soft gelatin capsule formulation of a 15-keto-prostaglandin compound, which comprises:

a soft gelatin capsule shell comprising gelatin and a sugar alcohol as a plasticizer, and

a mixture comprising a 15-keto-prostaglandin compound and a pharmaceutically acceptable vehicle, which is filled in the shell.

2. The formulation of claim **1**, wherein the 15-keto-prostaglandin compound is a compound of the formula (I):



(I)

wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is $—CH_3$, or $—CH_2OH$, $—COCH_2OH$, —COOH or a functional derivative thereof;

B is $—CH_2—CH_2—$, —CH═CH— or —C≡C—;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

Ra is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclicoxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclicoxy group.

3. The formulation of claim **1**, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-prostaglandin compound.

4. The formulation of claim **1**, wherein the 15-keto-prostaglandin compound is a 15-keto-16-mono or 16,16-di-halogen-prostaglandin compound.

5. The formulation of claim **1**, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16-mono- or 16,16-di-halogen-prostaglandin compound.

6. The formulation of claim **1**, wherein the 15-keto-prostaglandin compound is a 15-keto-16-mono- or 16,16-di-fluoro-prostaglandin compound.

7. The formulation of claim **1**, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16-mono- or 16,16-di-fluoro-prostaglandin compound.

8. The formulation of claim **1**, wherein the 15-keto-prostaglandin compound is a 15-keto-prostaglandin E compound.

9. The formulation of claim **1**, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E_1.

10. The formulation of claim **1**, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-18S-methyl-prostaglandin E_1.

11. The formulation of claim **1**, wherein the sugar alcohol is selected from the group consisting of sorbitol, maltitol, sugar alcohol solution derived from corn starch, hydrogenated maltose syrup and a mixture thereof.

12. The formulation of claim **1**, wherein the sugar alcohol comprises sorbitol and sorbitan as its major component.

13. A method for stabilizing a 15-keto-prostaglandin compound, which comprises: dissolving, dispersing or mixing the 15-keto-prostaglandin in a pharmaceutically acceptable vehicle to give a liquid mixture, and incorporating the liquid mixture in a soft gelatin capsule which comprises gelatin and a sugar alcohol as a plasticizer such that a soft gelatin capsule formulation of claim **1** is prepared.

14. A method for stabilizing a 15-keto-prostaglandin compound, which comprises encapsulating the compound together with a glyceride in a soft gelatin capsule shell comprising gelatin and a sugar alcohol as a plasticizer such that a soft gelatin capsule formulation of claim **1** is prepared.

15. The formulation of claim **1**, wherein the pharmaceutically acceptable vehicle is a medium chain fatty acid triglyceride.

16. The method of claim **14**, wherein the glyceride is a medium chain fatty acid triglyceride.

17. The formulation of claim **1**, wherein the pharmaceutically acceptable vehicle is a fatty acid ester or a polyol.

18. The formulation of claim **1**, wherein the pharmaceutically acceptable vehicle is glycerin or propylene glycol.

19. The formulation of claim **1**, wherein the pharmaceutically acceptable vehicle is a fatty acid ester or glycerin.

20. The formulation of claim **1**, wherein the pharmaceutically acceptable vehicle is a glyceride.

21. The formulation of claim **1**, wherein the pharmaceutically acceptable vehicle is a fatty acid ester.

22. The formulation of claim **1**, wherein the pharmaceutically acceptable vehicle is glycerin.

* * * * *

Exhibit H

US008338639B2

(12) **United States Patent**
Hashitera et al.

(10) **Patent No.: US 8,338,639 B2**
(45) **Date of Patent: *Dec. 25, 2012**

(54) **SOFT-GELATIN CAPSULE FORMULATION**

(75) Inventors: **Yukiko Hashitera**, Kobe (JP); **Ryu Hirata**, Sanda (JP); **Yasuhiro Harada**, Sanda (JP); **Ryuji Ueno**, Potomac, MD (US)

(73) Assignees: **Sucampo AG**, Zug (CH); **R-Tech Ueno, Ltd.**, Tokyo (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/210,556**

(22) Filed: **Aug. 16, 2011**

(65) **Prior Publication Data**

US 2011/0300211 A1 Dec. 8, 2011

Related U.S. Application Data

(63) Continuation of application No. 11/656,476, filed on Jan. 23, 2007, now Pat. No. 8,026,393.

(60) Provisional application No. 60/761,360, filed on Jan. 24, 2006.

(51) **Int. Cl.**
C07C 61/06 (2006.01)
C07C 61/20 (2006.01)

(52) **U.S. Cl.** **562/504**; 514/513

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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Primary Examiner — Yevegeny Valenrod
(74) *Attorney, Agent, or Firm* — Sughrue Mion, PLLC

(57) **ABSTRACT**

The present invention provides a soft gelatin capsule formulation of a 15-keto-prostaglandin compound, which includes: a soft gelatin capsule shell including gelatin and sugar alcohol as a plasticizer, and a mixture including a 15-keto-prostaglandin compound and a pharmaceutically acceptable vehicle which is filled in the shell. By encapsulating the 15-keto-prostaglandin compound in the specified soft gelatin capsule shell, stability of the compound is significantly improved.

23 Claims, No Drawings

SOFT-GELATIN CAPSULE FORMULATION

CROSS REFERENCE TO RELATED APPLICATIONS

This is a continuation of application Ser. No. 11/656,476 filed Jan. 23, 2007, and claims the benefit of U.S. Provisional Application No. 60/761,360 filed Jan. 24, 2006. The disclosure of application Ser. No. 11/656,476 is hereby incorporated by reference.

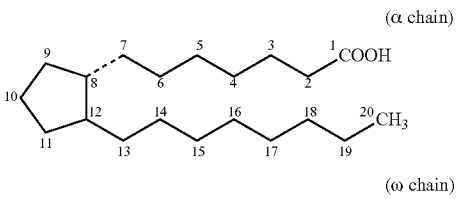
FIELD OF THE INVENTION

The present invention relates to a soft-gelatin capsule formulation of a therapeutically effective 15-keto-prostaglandin compound.

BACKGROUND ART

Prostaglandins (hereinafter, referred to as PGs) are members of class of organic carboxylic acids, which are contained in tissues or organs of human and other mammals, and exhibit a wide range of physiological activities. PGs found in nature (primary PGs) have, as a general structural property thereof, a prostanoic acid skeleton as shown in the formula (A):

(A)



On the other hand, some synthetic analogues have modified skeletons. The primary PGs are classified into PGAs, PGBs, PGCs, PGDs, PGEs, PGFs, PGGs, PGHs, PGIs and PGJs on the basis of the structural property of the five membered ring moiety, and further classified into the following three types by the number and position of the unsaturated bond in the carbon chain moiety.

Type 1 (subscript 1): 13,14-unsaturated-15-OH

Type 2 (subscript 2): 5,6- and 13,14-diunsaturated-15-OH

Type 3 (subscript 3): 5,6-, 13,14-, and 17,18-triunsaturated-15-OH.

Further, PGFs are classified on the basis of the configuration of the hydroxyl group at the 9-position into α type (wherein the hydroxyl group is of the α-configuration) and β type (wherein the hydroxyl group is of the β-configuration).

In addition, some 15-keto-PGs (PGs having an oxo group at position 15 in place of the hydroxy group) and 13,14-dihydro-15-keto-PGs have been known as substances naturally produced by enzymatic actions during metabolism of the primary PGs and have some therapeutic effect. 15-keto-PGs have been disclosed in U.S. Pat. Nos. 5,073,569, 5,534,547, 5,225,439, 5,166,174, 5,428,062 5,380,709 5,886,034 6,265,440, 5,106,869, 5,221,763, 5,591,887, 5,770,759 and 5,739,161. The contents of these publications are herein incorporated by reference.

For example, 15-keto-16-halogen prostaglandin compounds are useful as cathartics (U.S. Pat. No. 5,317,032, the contents of the reference is herein incorporated by reference). For treating gastrointestinal diseases, the agent is preferably formulated as an orally administrable dosage form. In general, PG compounds are less soluble in water and become significantly unstable under the presence of water. A capsulated formulation comprises a 15-keto-16-halogen PG compound and a solvent which can maintain the stability of the compound such as glyceride had been proposed (WO01/027099 (U.S. Pat. No. 6,583,174), the contents of the cited reference is herein incorporated by reference.

Elastic shell of a soft gelatin capsule, in general, incorporates a plasticizer in addition to gelatin. Examples of plasticizer include glycerin, propylene glycol, sorbitol, maltitol, sugar alcohol solution derived from corn starch (Anidrisorb™, Polysorb™), i.e. a mixture of sorbitol, sorbitane, mannitol and hydrogenated starch hydrolysate, hydrogenated maltose starch syrup, i.e. a mixture of maltitol, sorbitol and oligosaccharide alcohol.

SUMMARY OF THE INVENTION

An object of the present invention is to provide an orally administrable dosage form of a 15-keto-prostaglandin compound which has an excellent shelf stability.

Accordingly, the instant application provides a soft gelatin capsule formulation of a 15-keto-prostaglandin compound, which comprises:

a soft gelatin capsule shell comprising gelatin and a sugar alcohol as a plasticizer, and

a mixture comprising a 15-keto-prostaglandin compound and a pharmaceutically acceptable vehicle, which is filled in the shell.

The invention is also provides a method for improving stability of a 15-keto-prostaglandin compound which comprises, dissolving the 15-keto-prostaglandin in a pharmaceutically acceptable solvent and incorporating the solution in a soft-gelatin capsule whose shell comprises gelatin and a sugar alcohol as a plasticizer.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The nomenclature of the PG compounds used herein is based on the numbering system of prostanoic acid represented in the above formula (A).

The formula (A) shows a basic skeleton of the C-20 PG compound, but the present invention is not limited to those having the same number of carbon atoms. In the formula (A), the numbering of the carbon atoms which constitute the basic skeleton of the PG compounds starts at the carboxylic acid (numbered 1), and carbon atoms in the α-chain are numbered 2 to 7 towards the five-membered ring, those in the ring are 8 to 12, and those in the ω-chain are 13 to 20. When the number of carbon atoms is decreased in the α-chain, the number is deleted in the order starting from position 2; and when the number of carbon atoms is increased in the α-chain, compounds are named as substitution compounds having respective substituents at position 2 in place of carboxy group (C-1). Similarly, when the number of carbon atoms is decreased in the ω-chain, the number is deleted in the order starting from position 20; and when the number of carbon atoms is increased in the ω-chain, compounds are named as substitution compounds having respective substituents at position 20. Stereochemistry of the compounds is the same as that of the above formula (A) unless otherwise specified.

In general, each of PGD, PGE and PGF represents a PG compound having hydroxy groups at positions 9 and/or 11, but in the present specification and claims they also include those having substituents other than the hydroxyl groups at positions 9 and/or 11. Such compounds are referred to as

9-dehydroxy-9-substituted-PG compounds or 11-dehydroxy-11-substituted-PG compounds. A PG compound having hydrogen in place of the hydroxy group is simply named as 9- or 11-dehydroxy compound.

As stated above, the nomenclature of PG compounds is based on the prostanoic acid skeleton. However, in case the compound has a similar partial construction as a prostaglandin, the abbreviation of "PG" may be used. Thus, a PG compound of which a-chain is extended by two carbon atoms, that is, having 9 carbon atoms in the α-chain is named as 2-decarboxy-2-(2-carboxyethyl)-PG compound. Similarly, a PG compound having 11 carbon atoms in the α-chain is named as 2-decarboxy-2-(4-carboxybutyl)-PG compound. Further, a PG compound of which a-chain is extended by two carbon atoms, that is, having 10 carbon atoms in the ω-chain is named as 20-ethyl-PG compound. These compounds, however, may also be named according to the IUPAC nomenclatures.

The 15-keto-PG compound used in the present invention may be any derivative of a PG insofar as having an oxo group at position 15 in place of the hydroxy group, and may further include a compound having one double bond between positions 13 and 14 (15-keto-PG type 1 compound), two double bonds between positions 13 and 14, and positions and 6 (15-keto-PG type 2 compound), and three double bonds between positions 5 and 6, positions 13 and 14, and positions 17 and 18(15-keto-PG type 3 compound), and a derivative thereof wherein the bond between the positions and 14 is single bond, in place of the double bond (13,14-dihydro-15-keto-PG compound).

Examples of the analogue including substitution compounds or derivatives include a PG compound of which the carboxy group at the end of the alpha chain is esterified; physiologically acceptable salt thereof; an unsaturated derivative having a double bond between positions 2 and 3 or a triple bond between positions 5 and 6; PG compounds having substituent(s) on carbon atom(s) at position(s) 3, 5, 6, 16, 17, 18, 19 and/or 20; and PG compounds having lower alkyl or a hydroxy (lower) alkyl group at position 9 and/or 11 in place of the hydroxy group.

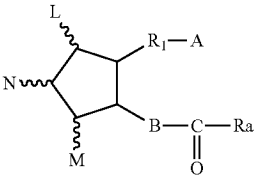
According to the present invention, preferred substituents on the carbon atom at position(s) 3, 17, 18 and/or 19 include alkyl having 1 to 6 carbon atoms, especially methyl and ethyl. Preferred substituents on the carbon atom at position 16 include lower alkyl such as methyl and ethyl, hydroxy, halogen atom such as chlorine and fluorine, and aryloxy such as trifluoromethylphenoxy. Preferred substituents on the carbon atom at position 17 include halogen atom such as chlorine and fluorine. Preferred substituents on the carbon atom at position 20 include saturated or unsaturated lower alkyl such as C_{1-4} alkyl, lower alkoxy such as C_{1-4} alkoxy, and lower alkoxy alkyl such as C_{1-4} alkoxy-C_{1-4} alkyl. Preferred substituents on the carbon atom at position 5 include halogen atoms such as chlorine and fluorine. Preferred substituents on the carbon atom at position 6 include an oxo group forming a carbonyl group. Stereochemistry of PGs having hydroxy, lower alkyl or hydroxy(lower)alkyl substituent on the carbon atom at positions 9 and 11 may be α, β or a mixture thereof.

Further, the above described derivatives may have a co chain shorter than that of the primary PGs and a substituent such as alkoxy, cyclohexyl, cyclohexyloxy, phenoxy and phenyl at the end of the truncated ω-chain.

Especially preferred compounds include a 13,14-dihydro-15-keto-PG compound that has a single bond between positions 13 and 14; a 15-keto-16-mono or 16,16-di-halogen PG compound that has at least one halogen atom, especially fluorine, at carbon atom of position 16; a 15-keto-PGE compound that has hydroxy group at position 9 and oxo group at position 11 of the five membered ring.

A preferred prostaglandin compound used in the present invention is represented by the formula (1):

(I)



wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is —CH_3, or —CH_2OH, —$COCH_2OH$, —COOH or a functional derivative thereof;

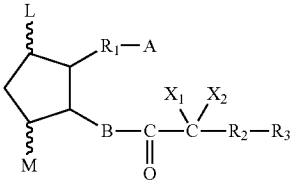
B is —CH_2—CH_2—, —CH═CH— or —C≡C—;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

Ra is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclicoxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower) alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclicoxy group.

A more preferred prostaglandin compound used in the present invention is represented by the formula (II):

(II)



wherein L and M are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have one or more double bonds;

A is —CH_3, or —CH_2OH, —$COCH_2OH$, —COOH or a functional derivative thereof;

B is —CH_2—CH_2—, —CH═CH— or —C≡C—;

X_1 and X_2 are hydrogen, lower alkyl, or halogen;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or het-

erocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur;

R_2 is a single bond or lower alkylene; and

R_3 is lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclicoxy group.

In the above formula, the term "unsaturated" in the definitions for R_1 and Ra is intended to include at least one or more double bonds and/or triple bonds that are isolatedly, separately or serially present between carbon atoms of the main and/or side chains. According to the usual nomenclature, an unsaturated bond between two serial positions is represented by denoting the lower number of the two positions, and an unsaturated bond between two distal positions is represented by denoting both of the positions.

The term "lower or medium aliphatic hydrocarbon" refers to a straight or branched chain hydrocarbon group having 1 to 14 carbon atoms (for a side chain, 1 to 3 carbon atoms are preferable) and preferably 1 to 10, especially 6 to 10 carbon atoms for R_1 and 1 to 10, especially, 1 to 8 carbon atoms for Ra.

The term "halogen" covers fluorine, chlorine, bromine and iodine.

The term "lower" is intended to include a group having 1 to 6 carbon atoms unless otherwise specified.

The term "lower alkyl" refers to a straight or branched chain saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl and hexyl.

The term "lower alkoxy" refers to a group of lower alkyl-O—, wherein lower alkyl is as defined above.

The term "hydroxy(lower)alkyl" refers to a lower alkyl as defined above which is substituted with at least one hydroxy group such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 1-methyl-1-hydroxyethyl.

The term "lower alkanoyloxy" refers to a group represented by the formula RCO—O—, wherein RCO— is an acyl group formed by oxidation of a lower alkyl group as defined above, such as acetyl.

The term "cyclo(lower)alkyl" refers to a cyclic group formed by cyclization of a lower alkyl group as defined above but contains three or more carbon atoms, and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cyclo(lower)alkyloxy" refers to the group of cyclo(lower)alkyl-O—, wherein cyclo(lower)alkyl is as defined above.

The term "aryl" may include unsubstituted or substituted aromatic hydrocarbon rings (preferably monocyclic groups), for example, phenyl, tolyl, xylyl. Examples of the substituents are halogen atom and halo(lower)alkyl, wherein halogen atom and lower alkyl are as defined above.

The term "aryloxy" refers to a group represented by the formula ArO—, wherein Ar is aryl as defined above.

The term "heterocyclic group" may include mono-to tricyclic, preferably monocyclic heterocyclic group which is 5 to 14, preferably 5 to 10 membered ring having optionally substituted carbon atom and 1 to 4, preferably 1 to 3 of 1 or 2 type of hetero atoms selected from nitrogen, oxygen and sulfur. Examples of the heterocyclic group include furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, 2-pyrrolinyl, pyrrolidinyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, piperidino, piperazinyl, morpholino, indolyl, benzothienyl, quinolyl, isoquinolyl, purinyl, quinazolinyl, carbazolyl, acridinyl, phenanthridinyl, benzimidazolyl, benzimidazolinyl, benzothiazolyl, phenothiazinyl. Examples of the substituent in this case include halogen, and halogen substituted lower alkyl group, wherein halogen atom and lower alkyl group are as described above.

The term "heterocyclicoxy group" means a group represented by the formula HcO-, wherein Hc is a heterocyclic group as described above.

The term "functional derivative" of A includes salts, preferably pharmaceutically acceptable salts, ethers, esters and amides.

Suitable "pharmaceutically acceptable salts" include salts formed with non-toxic bases conventionally used in pharmaceutical field, for example a salt with an inorganic base such as an alkali metal salt (such as sodium salt and potassium salt), an alkaline earth metal salt (such as calcium salt and magnesium salt), an ammonium salt; or a salt with an organic base, for example, an amine salt including such as methylamine salt, dimethylamine salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)ethane salt, monomethylmonoethanolamine salt, procaine salt and caffeine salt), a basic amino acid salt (such as arginine salt and lysine salt), tetraalkyl ammonium salt and the like. These salts may be prepared by a conventional process, for example from the corresponding acid and base or by salt interchange.

Examples of the ethers include alkyl ethers, for example, lower alkyl ethers such as methyl ether, ethyl ether, propyl ether, isopropyl ether, butyl ether, isobutyl ether, t-butyl ether, pentyl ether and 1-cyclopropyl ethyl ether; and medium or higher alkyl ethers such as octyl ether, diethyihexyl ether, lauryl ether and cetyl ether; unsaturated ethers such as oleyl ether and linolenyl ether; lower alkenyl ethers such as vinyl ether, allyl ether; lower alkynyl ethers such as ethynyl ether and propynyl ether; hydroxy(lower)alkyl ethers such as hydroxyethyl ether and hydroxyisopropyl ether; lower alkoxy(lower)alkyl ethers such as methoxymethyl ether and 1-methoxyethyl ether; optionally substituted aryl ethers such as phenyl ether, tosyl ether, t-butylphenyl ether, salicyl ether, 3,4-di-methoxyphenyl ether and benzamidophenyl ether; and aryl(lower)alkyl ethers such as benzyl ether, trityl ether and benzhydryl ether.

Examples of the esters include aliphatic esters, for example, lower alkyl esters such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester and 1-cyclopropylethyl ester; lower alkenyl esters such as vinyl ester and allyl ester; lower alkynyl esters such as ethynyl ester and propynyl ester; hydroxy(lower) alkyl ester such as hydroxyethyl ester; lower alkoxy (lower) alkyl esters such as methoxymethyl ester and 1-methoxyethyl ester; and optionally substituted aryl esters such as, for example, phenyl ester, tolyl ester, t-butylphenyl ester, salicyl ester, 3,4-di-methoxyphenyl ester and benzamidophenyl ester; and aryl(lower)alkyl ester such as benzyl ester, trityl ester and benzhydryl ester.

The amide of A means a group represented by the formula -CONR'R", wherein each of R' and R" is hydrogen, lower alkyl, aryl, alkyl- or aryl-sulfonyl, lower alkenyl and lower alkynyl, and include for example lower alkyl amides such as methylamide, ethylamide, dimethylamide and diethylamide; arylamides such as anilide and toluidide; and alkyl- or aryl-

sulfonylamides such as methylsulfonylamide, ethylsulfonylamide and tolylsulfonylamide.

Preferred examples of L and M include hydroxy and oxo, and especially, M is hydroxy and L is oxo which has a 5-membered ring structure of, so called, PGE type.

Preferred example of A is —COOH, its pharmaceutically acceptable salt, ester or amide thereof.

Preferred example of B is —CH_2—CH_2—, which provide the structure of so-called, 13,14-dihydro type.

Preferred example of X_1 and X_2 is that at least one of them is halogen, more preferably, both of them are halogen, especially, fluorine that provides a structure of, so called 16,16-difluoro type.

Preferred R_1 is a hydrocarbon residue containing 1-10 carbon atoms, preferably 6 to 10 carbon atoms. Further, at least one carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur.

Examples of R_1 include, for example, the following groups:

—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH═CH—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH═CH—,
—CH_2—C≡C—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH (CH_3)—CH_2—,
—CH_2—CH_2—CH_2—CH_2—O—CH_2—,
—CH_2—CH═CH—CH_2—O—CH_2—,
—CH_2—C≡C—CH_2—O—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH═CH—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—CH═CH—,
—CH_2—C≡C—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—CH (CH_3)—CH_2—,
—CH_2—CH_2—CH_2—CH_2CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH═CH—CH_2—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH═CH—,
—CH_2—CH≡C—CH_2—CH_2—CH_2—CH_2—CH_2—, and
—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH (CH_3)—CH_2—.

Preferred Ra is a hydrocarbon containing 1 to 10 carbon atoms, more preferably, 1 to 8 carbon atoms. Ra may have one or two side chains having one carbon atom.

The configuration of the ring and the α- and/or ω chains in the above formula (I) and (II) may be the same as or different from that of the primary PGs. However, the present invention also includes a mixture of a compound having a primary type configuration and a compound of a non-primary type configuration.

The typical example of the present compounds are 13, 14-dihydro-15-keto-16-mono- or 16, 16-di-fluoro PGE compound and its derivative or analogue.

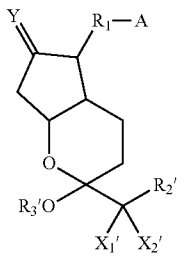
In the present invention, the 15-keto-PG compound may be in the keto-acetal equilibrium by formation of a hemiacetal between hydroxy at position 11 and keto at position 15.

For example, it has been revealed that when both of X_1 and X_2 are halogen atoms, especially, fluorine atoms, the compound contains a tautomeric isomer, bi-cyclic compound.

If such tautomeric isomers as above are present, the proportion of both tautomeric isomers varies with the structure of the rest of the molecule or the kind of the substituent present. Sometimes one isomer may predominantly be present in comparison with the other. However, it is to be appreciated that the present invention includes both isomers.

Further, the 15-keto-PG compounds used in the invention include the bi-cyclic compound and analogs or derivatives thereof.

The bi-cyclic compound is represented by the formula (III):



(III)

wherein, A is —CH_3, or —CH_2OH, —$COCH_2OH$, —COOH or a functional derivative thereof;

X_1' and X_2'are hydrogen, lower alkyl, or halogen;

Y is

wherein R_4'and R_5' are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl,

wherein R_4'and R_5' are not hydroxy and lower alkoxy at the same time;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur;

R_2' is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclicoxy group; lower alkyl; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclicoxy group; and

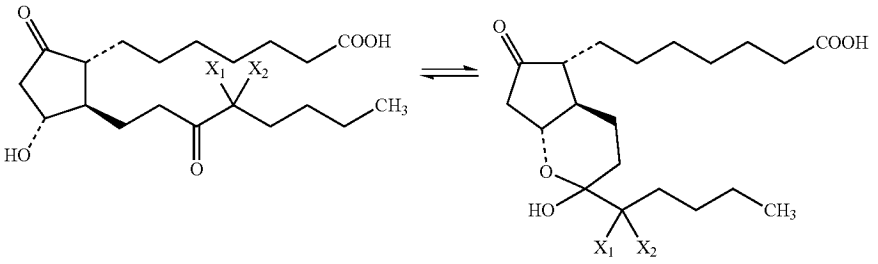
R_3' is hydrogen, lower alkyl, cyclo(lower)alkyl, aryl or heterocyclic group.

Furthermore, while the compounds used in the invention may be represented by a formula or name based on keto-type regardless of the presence or absence of the isomers, it is to be noted that such structure or name does not intend to exclude the acetal type compound.

In the present invention, any of isomers such as the individual tautomeric isomers, the mixture thereof, or optical isomers, the mixture thereof, a racemic mixture, and other steric isomers may be used in the same purpose.

Some of the compounds used in the present invention may be prepared by the method disclosed in U.S. Pat. Nos. 5,073,569, 5,166,174, 5,221,763, 5,212,324, 5,739,161 and 6,242,485, the contents of these references are herein incorporated by reference.

It has been known that 13,14-dihydro-15-keto-prostaglandin compound having the formula as shown below (Tautomer I) may be in equilibrium with its tautomeric isomer (tautomer II) (See U.S. Pat. Nos. 5,166,174, 5,225,439, 5,284,858, 5,380,709, 5,428,062 and 5,886,034, the contents of these references are herein incorporated by reference.)

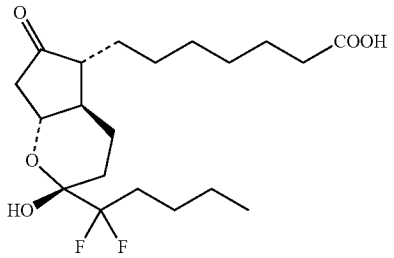


Tautomer I Tautomer II

It is considered that the halogen atom(s) at X_1 and/or X_2 promote bi-cyclic ring formation, such as the compound 1 or 2 below. In addition, in the absence of water, the tautomeric compounds as above exist predominantly in the form of the bi-cyclic compound. In aqueous media, it is supposed that hydrogen bonding occurs between the water molecule and, for example, the keto group on the hydrocarbon chain, thereby hindering bi-cyclic ring formation. The bi-cyclic/mono-cyclic structures, for example, may be present in a ratio of 6:1 in D_2O; 10:1 in CD_3OD-D_2O and 96:4 in $CDCl_3$. In the instant specification and claims, tautomeric mixture containing the bi-cyclic compound in a ratio even greater to substantially 100% bi-cyclic compound is within this invention.

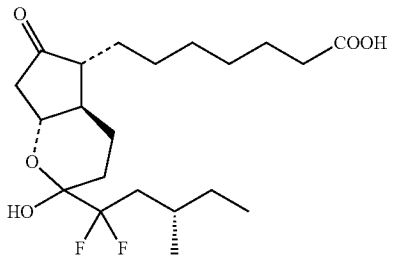
Embodiment of the bi-cyclic compound of the present invention include the Compounds 1 and 2 shown below.

Compound 1:



7- [(2R, 4aR, 5R, 7aR)-2-(1, 1-difluoropentyl)-2-hydroxy-6-oxpoctahydrocyclopenta[b]pyran-5-yl]heptanoic acid

Compound 2:



7-{(4aR, 5R, 7aR)-2-[(3S)-1,1-difluoro-3-methylpentyl]-2-hydroxy-6-oxooctahydrocyclopenta[b]pyran-5-yl}heptanoic acid

According to the present invention, the pharmaceutically acceptable vehicle is not specifically limited as long as the vehicle can disperse the 15-keto-PG therein and does not significantly deteriorate the stability of the compound. In view of manufacturing soft gelatin capsule formulation, a solvent which is liquid at the room temperature. A solution, dispersion or mixture of the 15-keto-PG in the solvent may be filled in the capsule.

Examples of the pharmaceutically acceptable vehicles preferably used in the instant invention may be fatty acid esters, i.e. an ester of fatty acid and an alcohol, and polyols.

Preferred fatty acid which consists the fatty acid ester is a medium or higher chain fatty acid having at least C6, preferably C6-24 carbon atoms, for example caproic acid (C6), caprylic acid(C8), capric acid(C10), lauric acid(C12) and myristic acid (C14), palmitic acid(C16), palmitoleic acid (C16), stearic acid(C18), oleic acid(C18), linoleic acid(C18), linolenic acid(C18), ricinolic acid(C18) and arachic acid (020). Preferred alcohols which consists the fatty acid ester may comprise C1-6 monovalent alcohol and polyols such as glycerin, polyethylene glycol and propylene glycol.

Preferred fatty acid esters may include a glyceride of a saturated or unsaturated fatty acid which may have a branched chain and a propylene glycol fatty acid ester. Two or more glycerides may be used as a mixture.

Examples of the mixture of glycerides are mixture of caprylic acid triglyceride and capric acid triglyceride, vegetable oils such as castor oil, corn oil, olive oil, sesame oil, rape oil, salad oil, cottonseed oil, camellia oil, peanut oil, palm oil and sunflower oil.

A fatty acid ester derived from a fatty acid and a monovalent alcohol is also preferably used as a pharmaceutically acceptable vehicle. The fatty acid ester may preferably be an ester of C8-20 fatty acid and a C2-3 monovalent alcohol, such as isopropyl myristate, isopropyl palmitate, ethyl linoleate and ethyl oleate.

Examples of polyols may preferably include alcohols having two or three hydroxy groups such as glycerin, polyethylene glycol and propylene glycol.

According to the present invention, the mixture which is filled in the soft-gelatin capsule shell may be obtained by dissolving or dispersing the above-described 15-keto-prostaglandin compound in the above described pharmaceutically acceptable vehicle which is liquid at the room temperature. When it is difficult to dissolve the 15-keto-PG compound directly in the vehicle, each of them may be dissolved in a solvent in which both of them are soluble respectively, and then the solutions may be combined.

The amount of the solvent in the mixture relative to the amount of the 15-keto-PG compound is not limited as long as

the 15-keto-PG is stable in the final formulation. In general, the amount of the vehicle per one part of the 15-keto-PG compound may be 1-5,000,000, preferably, 5-1,000,000 and most preferably, 10-500,000 parts by weight.

The mixture used in the invention may further comprise an oil solvent such as mineral oil, liquid paraffin, and tocopherol. The mixture of the present invention may further comprise another pharmaceutically active ingredient.

In a preferred embodiment, the composition of the present invention is substantially free of water. The term "substantially free of water" means that the composition does not contain water that is intentionally added. It is understood that many materials contain water that is taken up from the atmosphere or is present as a coordination complex in its normal state. Water taken up by hygroscopic materials or present as a hydrate is permissibly present in the compositions of this embodiment. According to the embodiment, any water that is present in the composition should not be present in amounts such that the water will have a deleterious effect to the composition of the present invention.

According to the present invention, the shell of the soft gelatin capsule is manufactured from gelatin and a sugar alcohol as a plasticizer.

Sugar alcohol used in the present invention is an alcohol obtained by hydrogen reduction of the aldehyde group of a saccharide. For example, sorbitol, mannitol, maltitol, lactitol, palatinit, xylitol, erithyritol, sugar alcohol solution derived from corn starch, i.e. a mixture of sorbitol, sorbitan, mannitol and hydrogenated starch hydrolysate, hydrogenated maltose starch syrup, i.e. a mixture of maltitol, sorbitol and oligosaccharide alcohol. Preferred sugar alcohols may include sorbitol, maltitol, sugar alcohol solution derived from corn starch and hydrogenated maltose starch syrup. Especially, sugar alcohol solution derived from corn starch and available on market under the name "Anidrisorb™" or "Polysorb™" is preferably used.

According to the invention, the amount of the sugar alcohol used for preparing the shell of the soft gelatin capsule is not specifically limited as long as the physical properties of the resulting capsule is not deteriorated. In general, the amount of sugar alcohol plasticizer is 20 to 60 parts by weight, preferably, 30 to 50 parts by weight per 100 parts by weight of gelatin.

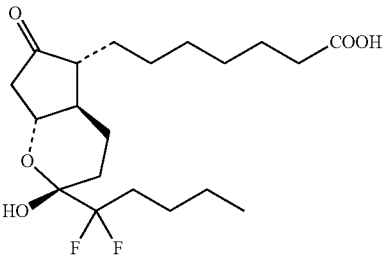
The soft gelatin capsule formulation of the 15-keto-PG compound may be manufactured according to a conventional manner using the above described liquid mixture and a mixture of gelatin and the plasticizer.

The present invention will be explained in more detail by means of the following examples, which are illustrated by way of example only and never intended to limit the scope of the present invention.

REFERENCE EXAMPLE 1

Compound 1 was dissolved in a vehicle shown in table 1 below to give 240 μg/g solution (sample). The precise concentration of compound 1 in the sample was determined by means of HPLC (day 0). Then, the sample was put in a hard grass container and kept at 55° C. for 10 days, and then the precise concentration of the compound 1 in the sample was determined by means of HPLC (day 10).

Compound 1



The determination of the concentration of the compound in the sample was carried out as follows. About 0.2 g of the sample was mixed with exactly 2 ml of internal standard solution and then with a dissolving agent shown in Table 1 to give 5 mL of sample solution. About 12 mg of the reference standard compound 1 was weighted precisely and added with acetonitrile to give exactly 100 ml solution. Exactly 0.8 ml of the solution was obtained and added with exactly 4 ml of the internal standard solution, and then added with the dissolving agent to give 10 ml of standard solution.

The fluorescent labeling agent was added to the respective solution, stirred and stood at room temperature. Then, respective solution in an amount that theoretically gives 3.6 ng of compound 1 was loaded on the column and analyzed under the condition as follows:

HPLC analysis condition:

Column: 5mm×25 cm stainless steel column packed with octadecylsilane treated silica gel for HPLC (511m)

Mobile phase: mixture of acetonitrile HPLC grade: methanol HPLC grade: ammonium acetate (0.05 mol/L)

Temperature: 35° C.

Detector: spectrophotofluorometer

Results are shown in Table 1:

TABLE 1

Assay results of compound 1 after 55° C. storage

	vehicle	dissolving agent	concentration of compound 1[1)] day 0	day 10
1	hydrogenated maltose starch syrup	acetonitrile/ Water (1:1)	—	24.4%
2	Sugar alcohol solution derived from corn starch[2)]	methanol	—	26.2%
3	glycerin	methanol	92.0%	78.0%
4	propylene glycol	acetonitrile	97.8%	88.6%
5	polyethylene glycol 400	acetonitrile	98.2%	90.1%

[1)]Percentage based on a theoretical amount (240 μg/g)
[2)]Polysorb 85/70/00 ™, ROQUETTE AMERICA, Inc.

EXAMPLE 1

One hundred (100) parts by weight of gelatin (type A, high bloom, SKW Biosystems #195F) and 35 parts by weight of a plasticizer shown in Table 2 were mixed in water and dried to give gelatin piece. Compound 1 was dissolved in medium

chain fatty acid triglyceride (USP/NF grade) to give a liquid mixture comprising 60 μg/g of the compound. 0.5 g of the liquid mixture and 0.5 g of each gelatin piece were put together in a sealed container and kept at 40° C. for 21 days. Then, the concentration of compound 1 contained in the liquid mixture was determined in the same manner as Reference Example 1. Results are shown in Table 2:

TABLE 2

Stability data of compound 1/medium chain fatty acid triglyceride (MCT) solution (60 μg/g)

gelatin piece		concentration
plasticizer	water content (after dried)	of compound 1 after storage[1)]
glycerin	23%	86.8%
sugar alcohol solution derived from corn starch[2)]	25%	92.0%

[1)]Percentage based on a theoretical amount (60 μg/g)
[2)]Polysorb 85/70/00 ™, ROQUETTE AMERICA, Inc.

According to the reference example 1, in case the 15-keto-prostaglandin compound of the invention and the sugar alcohol were contacted directly, stability of the compound was significantly lowered. In contrast, in case the 15-keto-PG compound was directly contacted with a polyol such as glycerin, the stability of the compound was maintained. It have surprisingly revealed by Example 1 that the stability of the 15-keto-prostaglandin contacted with gelatin piece prepared using sugar alcohol as a plasticizer was better than that contacted with gelatin piece with glycerin as a plasticizer.

EXAMPLE 2

Sugar alcohol solution derived from corn starch in an amount shown in Table 3 was added in an appropriate amount of water, stirred and heated. Then, gelatin 100 parts by weight was added thereto to give gelatin solution. Compound 1 was dissolved in medium chain fatty acid triglyceride (USP/NF grade) to give a fill solution containing 240 μg/g of compound 1. The gelatin solution and the liquid mixture were loaded on capsule forming and filling machine to give capsule containing the fill solution therein, and the capsule was dried to give soft gelatin capsule.

The capsule was put in a sealed container and kept at 40° C. for 3 months. The concentration of compound 1 in the fill solution contained in the capsule was determined after 1, 2 and 3 months storage in the same manner as Reference Example 1.

TABLE 3

Stability of soft gelatin capsule of compound 1

soft gelatin capsule (parts by weight)				conc. (% of Initial) 40° C. 1 mo	2 mo	3 mo
gelatin	100	sugar alcohol solution[1)]	35	99.9%	100.3%	99.2%
			45	—	100.5%	100.0%
			55	—	99.3%	100.0%

[1)]Polysorb 85/70/00 ™, ROQUETTE AMERICA, Inc., derived from corn starch

What is claimed is:

1. A soft gelatin capsule formulation of a 15-keto-prostaglandin compound, which comprises:

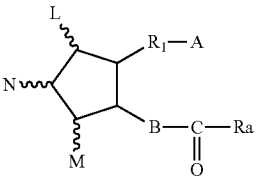
a soft gelatin capsule shell comprising gelatin and a sugar alcohol as a plasticizer, and

a mixture comprising a 15-keto-prostaglandin compound and a pharmaceutically acceptable vehicle, which is filled in the shell,

wherein the pharmaceutically acceptable vehicle is a fatty acid ester or a polyol,

wherein the 15-keto-prostaglandin compound is a compound of the formula (I):

(I)



wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is —CH_3, or —CH_2OH, —$COCH_2OH$, —COOH or a functional derivative thereof;

B is —CH_2—CH_2—, —CH═CH— or —C≡C—;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

Ra is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclicoxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclicoxy group.

2. The formulation of claim **1**, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-prostaglandin compound.

3. The formulation of claim **1**, wherein the 15-keto-prostaglandin compound is a 15-keto-16-mono or 16,16-di-halogen-prostaglandin compound.

4. The formulation of claim **1**, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16-mono-or 16,16-di-halogen-prostaglandin compound.

5. The formulation of claim **1**, wherein the 15-keto-prostaglandin compound is a 15-keto-16-mono- or 16,16-di-fluoro-prostaglandin compound.

6. The formulation of claim **1**, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16-mono-or 16,16-di-fluoro-prostaglandin compound.

7. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 15-keto-prostaglandin E compound.

8. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E_1.

9. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-18S-methyl-prostaglandin E_1.

10. The formulation of claim 1, wherein the sugar alcohol is selected from the group consisting of sorbitol, maltitol, sugar alcohol solution derived from corn starch, hydrogenated maltose syrup and a mixture thereof.

11. The formulation of claim 1, wherein the sugar alcohol comprises sorbitol and sorbitan as its major component.

12. The formulation of claim 1, wherein the pharmaceutically acceptable vehicle is a fatty acid ester.

13. The formulation of claim 1, wherein the pharmaceutically acceptable vehicle is a polyol.

14. The formulation of claim 1, wherein the pharmaceutically acceptable vehicle is glycerin or propylene glycol.

15. The formulation of claim 10, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E_1.

16. The formulation of claim 11, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E_1.

17. The formulation of claim 12, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E_1.

18. The formulation of claim 13, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E_1.

19. The formulation of claim 14, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E_1.

20. The formulation of claim 1, wherein the sugar alcohol comprises sorbitol,

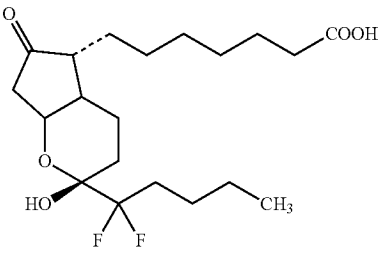
wherein the pharmaceutically acceptable vehicle comprises a fatty acid ester, and

wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E_1.

21. A soft gelatin capsule formulation comprising:

a soft gelatin capsule shell comprising gelatin and a sugar alcohol as a plasticizer, and

a mixture comprising



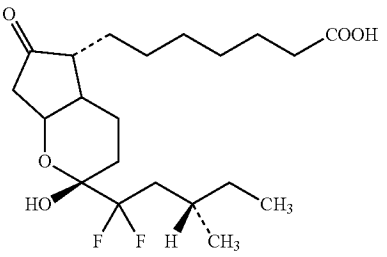
and a pharmaceutically acceptable vehicle, which is filled in the shell,

wherein the pharmaceutically acceptable vehicle is a fatty acid ester or a polyol.

22. A soft gelatin capsule formulation comprising:

a soft gelatin capsule shell comprising gelatin and a sugar alcohol as a plasticizer, and

a mixture comprising



and a pharmaceutically acceptable vehicle, which is filled in the shell,

wherein the pharmaceutically acceptable vehicle is a fatty acid ester or a polyol.

23. The formulation of claim 1, wherein M is a group other than hydrogen.

* * * * *

Exhibit I

US008748481B2

(12) **United States Patent**
Ueno

(10) **Patent No.: US 8,748,481 B2**
(45) **Date of Patent: Jun. 10, 2014**

(54) **METHOD FOR TREATING GASTROINTESTINAL DISORDER**

(75) Inventor: **Ryuji Ueno**, Montgomery, MD (US)

(73) Assignee: **Sucampo AG**, Zug (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **11/216,012**

(22) Filed: **Sep. 1, 2005**

(65) **Prior Publication Data**

US 2006/0063830 A1 Mar. 23, 2006

Related U.S. Application Data

(60) Provisional application No. 60/606,521, filed on Sep. 2, 2004, provisional application No. 60/666,317, filed on Mar. 30, 2005, provisional application No. 60/666,593, filed on Mar. 31, 2005.

(51) **Int. Cl.**
A61K 31/352 (2006.01)

(52) **U.S. Cl.**
USPC **514/456**; 514/892

(58) **Field of Classification Search**
None
See application file for complete search history.

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Primary Examiner — Savitha Rao
Assistant Examiner — Gregg Polansky
(74) *Attorney, Agent, or Firm* — Sughrue Mion, PLLC

(57) **ABSTRACT**

The present invention relates to a method for the long term treatment of gastrointestinal disorders in a human subject, which comprises administering an effective amount of a halogenated prostaglandin compound and/or its tautomer to the subject. The method induces substantially no electrolyte shifting during the term of the treatment. The compound used in the present invention can improve quality of life in the human subjects with gastrointestinal disorders, are similarly effective in treating male and female subjects, and also effective in a human subject aged even 65 years and older.

17 Claims, 7 Drawing Sheets

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FIG. 1

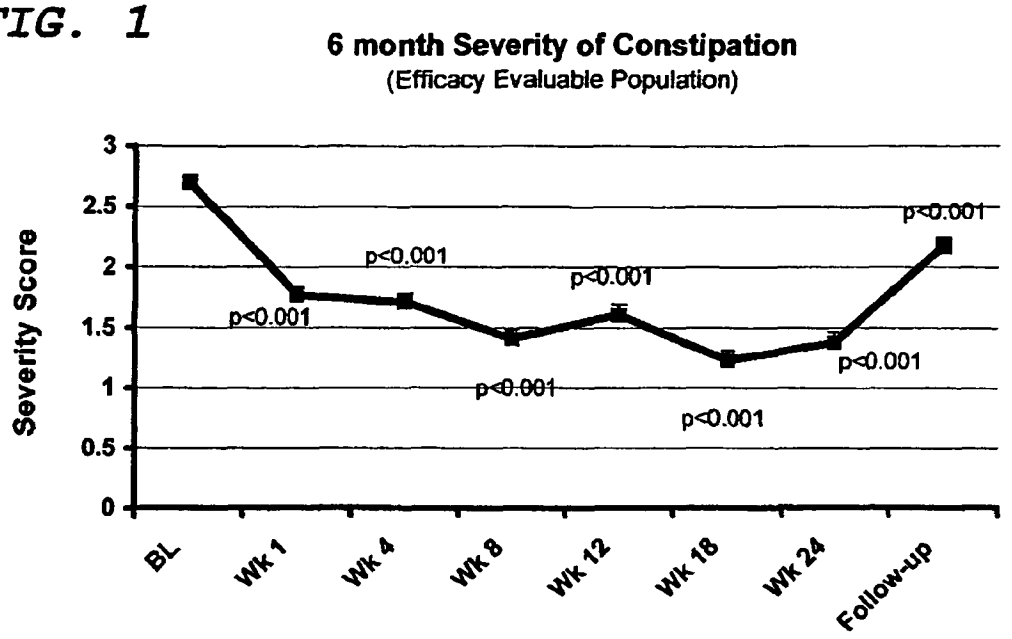

6 month Severity of Constipation
(Efficacy Evaluable Population)
Severity Score
3
2.5
2
1.5
1
0.5
0
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
BL
Wk 1
Wk 4
Wk 8
Wk 12
Wk 18
Wk 24
Follow-up

FIG. 2

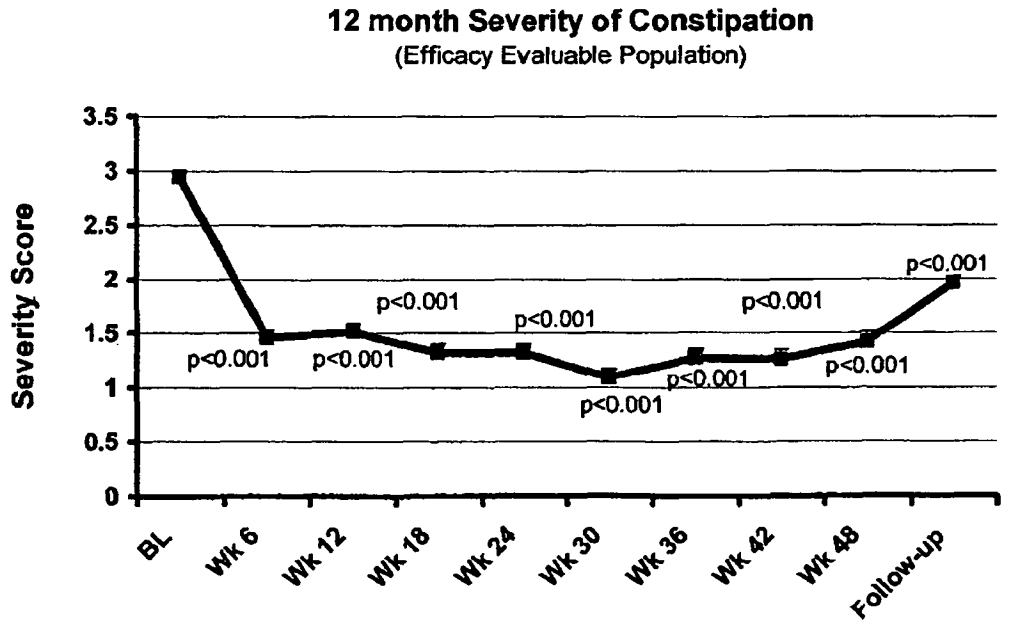

12 month Severity of Constipation
(Efficacy Evaluable Population)
Severity Score
3.5
3
2.5
2
1.5
1
0.5
0
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
BL
Wk 6
Wk 12
Wk 18
Wk 24
Wk 30
Wk 36
Wk 42
Wk 48
Follow-up

FIG. 3

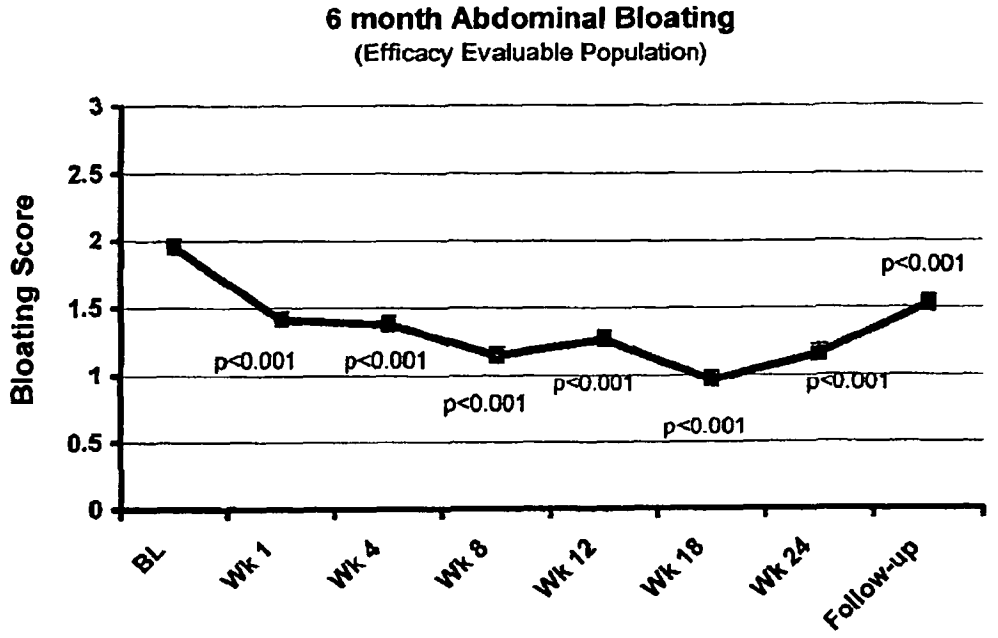

6 month Abdominal Bloating
(Efficacy Evaluable Population)
Bloating Score
3
2.5
2
1.5
1
0.5
0
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
BL
Wk 1
Wk 4
Wk 8
Wk 12
Wk 18
Wk 24
Follow-up

FIG. 4

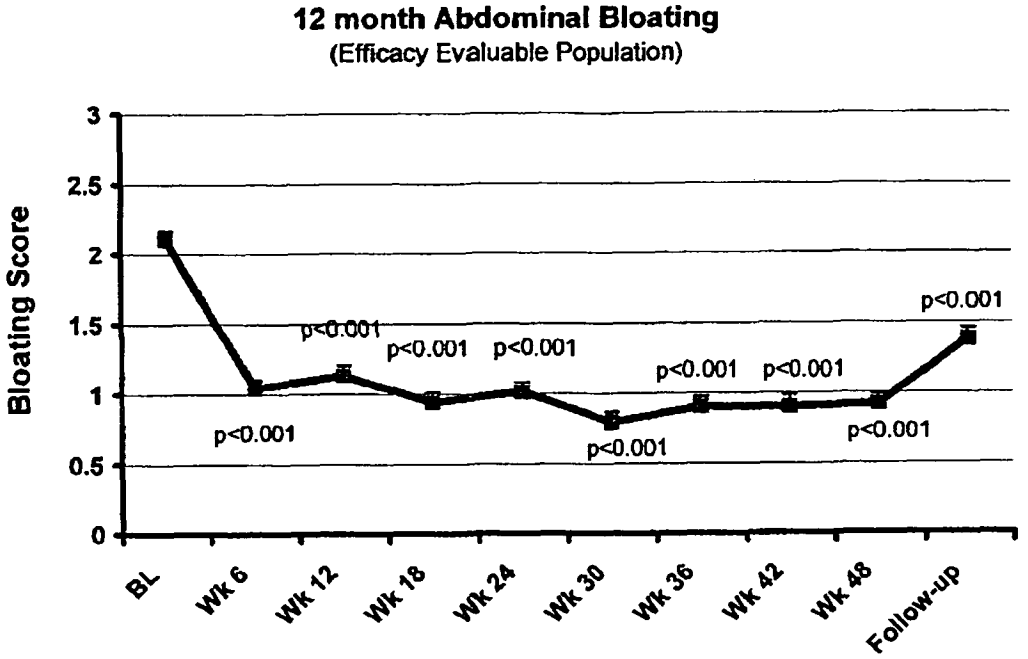

12 month Abdominal Bloating
(Efficacy Evaluable Population)
Bloating Score
3
2.5
2
1.5
1
0.5
0
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
BL
Wk 6
Wk 12
Wk 18
Wk 24
Wk 30
Wk 36
Wk 42
Wk 48
Follow-up

FIG. 5

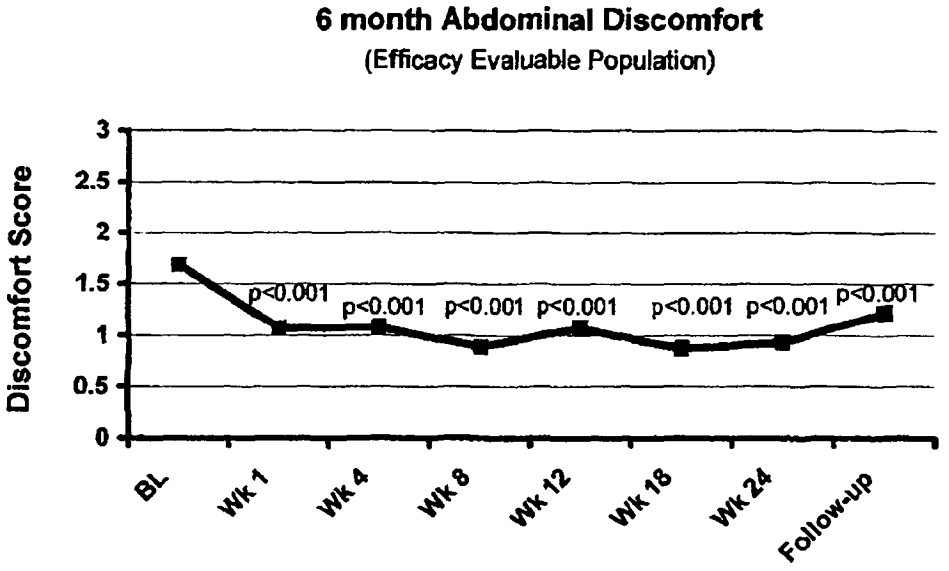

6 month Abdominal Discomfort
(Efficacy Evaluable Population)
Discomfort Score
3
2.5
2
1.5
1
0.5
0
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
BL
Wk 1
Wk 4
Wk 8
Wk 12
Wk 18
Wk 24
Follow-up

FIG. 6

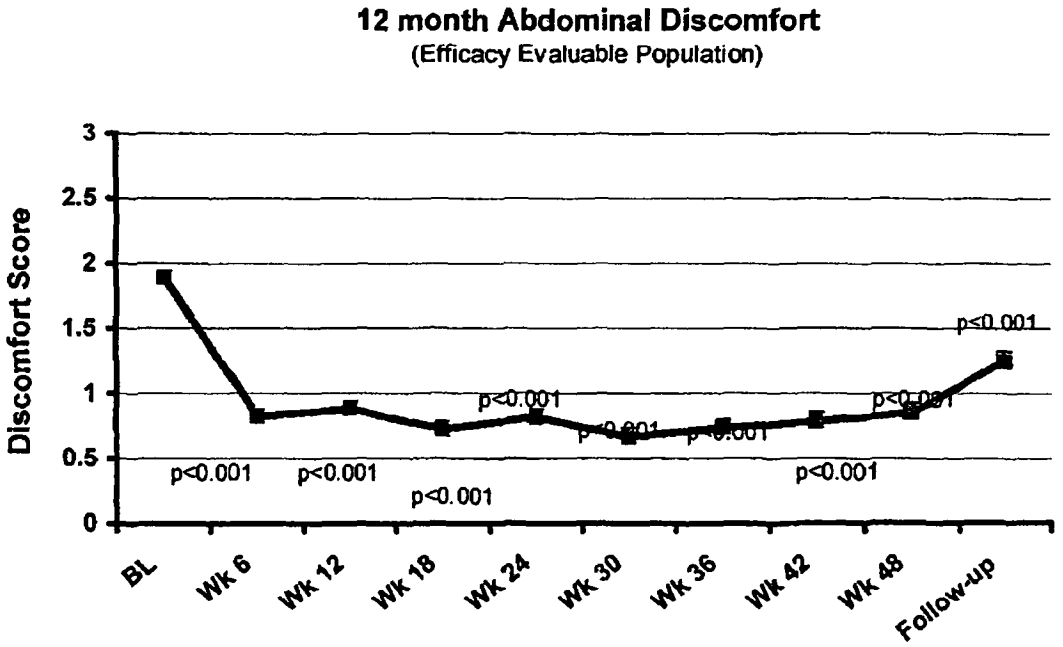

12 month Abdominal Discomfort
(Efficacy Evaluable Population)
Discomfort Score
3
2.5
2
1.5
1
0.5
0
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
BL
Wk 6
Wk 12
Wk 18
Wk 24
Wk 30
Wk 36
Wk 42
Wk 48
Follow-up

FIG. 7

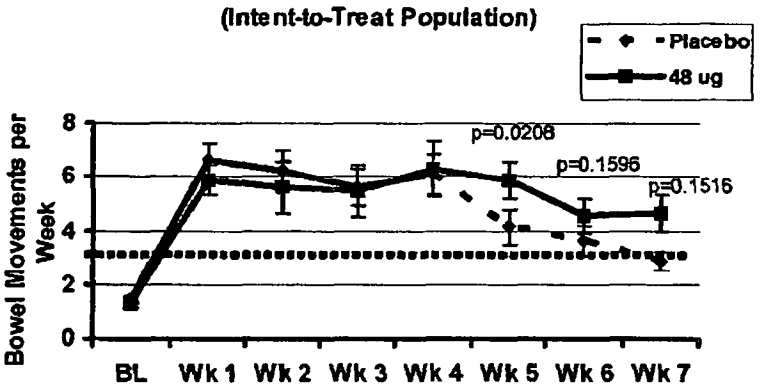

(Intent-to-Treat Population)
Placebo
48 ug
Bowel Movements per Week
8
6
4
2
0
p=0.0208
p=0.1596
p=0.1516
BL
Wk 1
Wk 2
Wk 3
Wk 4
Wk 5
Wk 6
Wk 7

FIG. 8

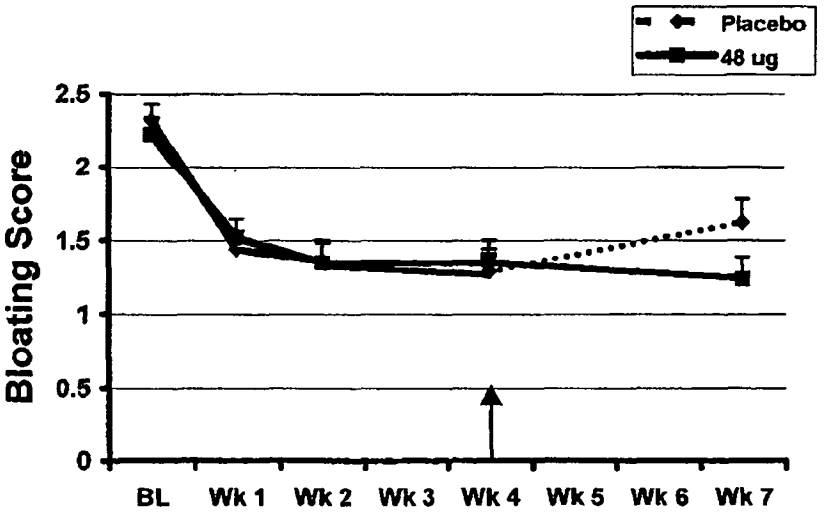

Placebo
48 ug
Bloating Score
2.5
2
1.5
1
0.5
0
BL
Wk 1
Wk 2
Wk 3
Wk 4
Wk 5
Wk 6
Wk 7

FIG. 9

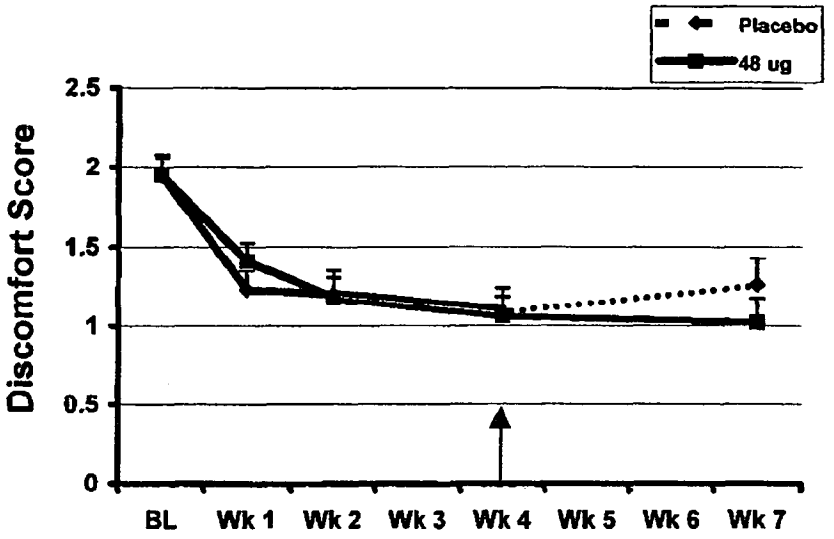

Placebo
48 ug
Discomfort Score
2.5
2
1.5
1
0.5
0
BL
Wk 1
Wk 2
Wk 3
Wk 4
Wk 5
Wk 6
Wk 7

FIG. 10

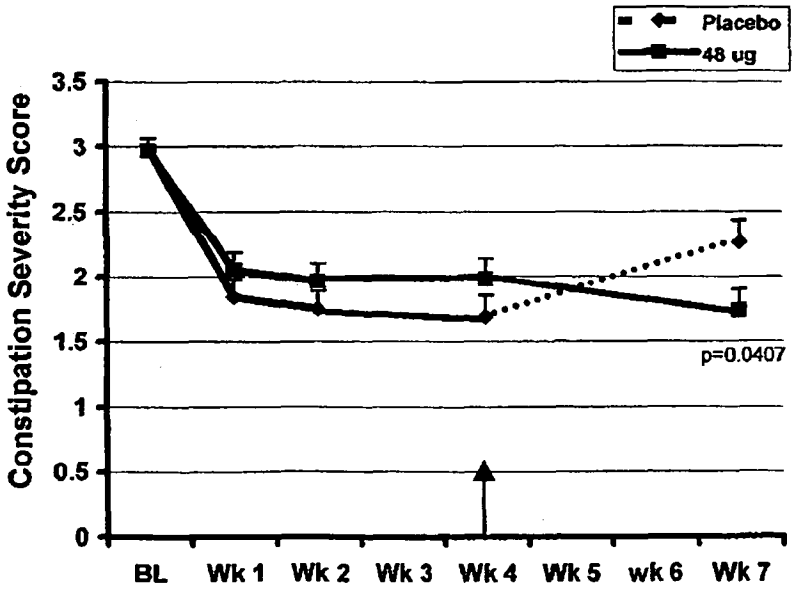

Placebo
48 ug
Constipation Severity Score
3.5
3
2.5
2
1.5
1
0.5
0
p=0.0407
BL
Wk 1
Wk 2
Wk 3
Wk 4
Wk 5
wk 6
Wk 7

FIG. 11

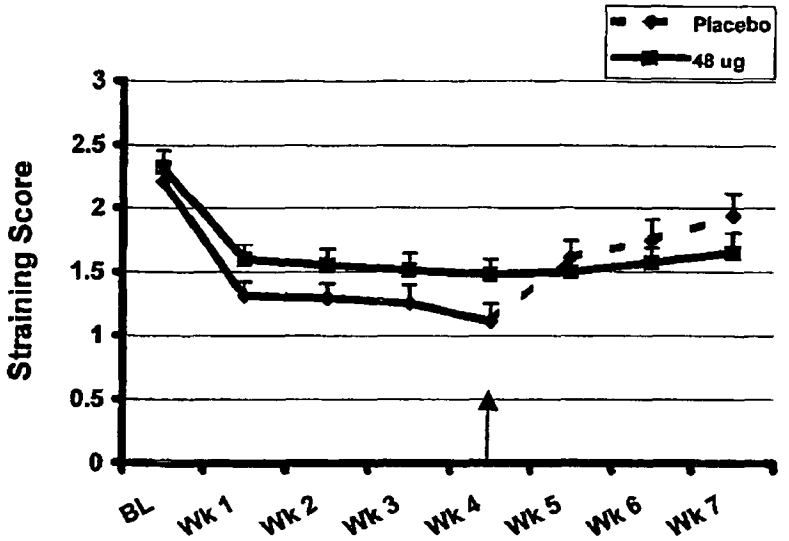

Placebo
48 ug
Straining Score
3
2.5
2
1.5
1
0.5
0
BL
Wk 1
Wk 2
Wk 3
Wk 4
Wk 5
Wk 6
Wk 7

FIG. 12

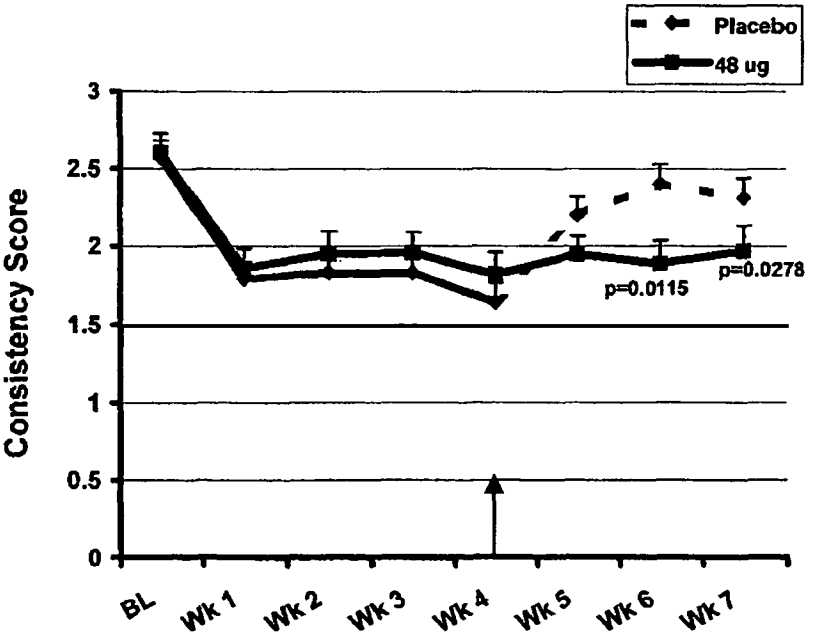

Placebo
48 ug
Consistency Score
3
2.5
2
1.5
1
0.5
0
p=0.0115
p=0.0278
BL
Wk 1
Wk 2
Wk 3
Wk 4
Wk 5
Wk 6
Wk 7

FIG. 13

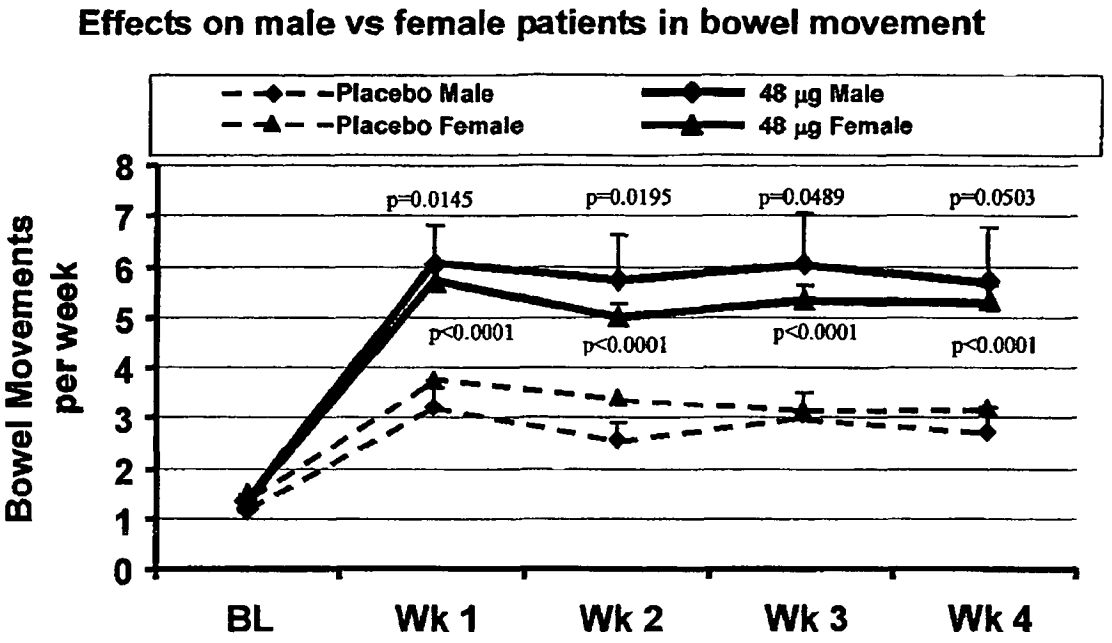
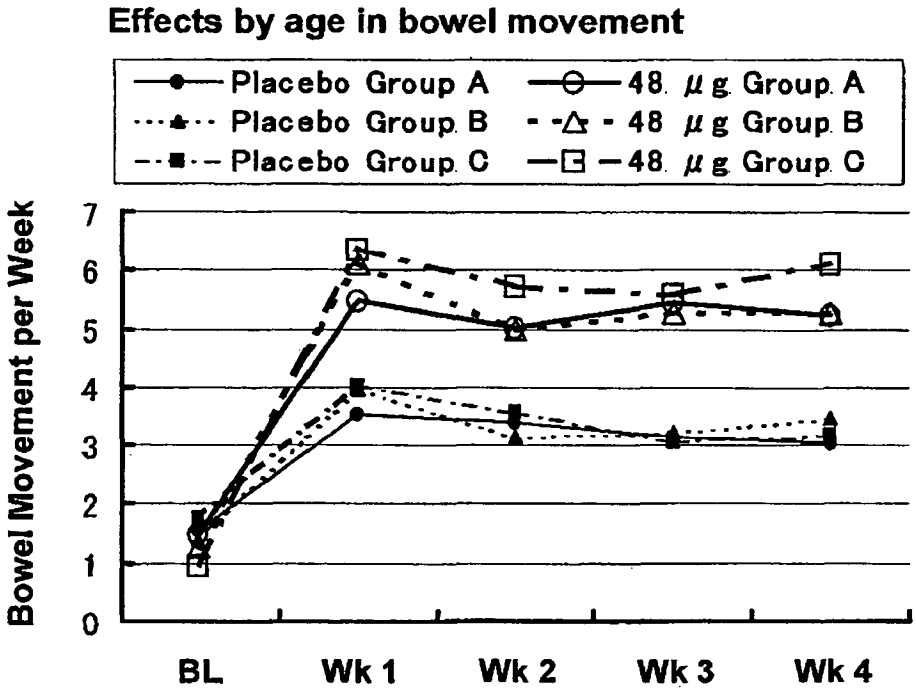


FIG. 14



Group A: 18≤Age<50, Group B: 50≤Age<65, Group C: 65≤Age

METHOD FOR TREATING GASTROINTESTINAL DISORDER

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims benefit from U.S. Provisional Application No. 60/606,521 filed on Sep. 2, 2004, U.S. Provisional Application No. 60/666,317 filed on Mar. 30, 2005, and U.S. Provisional Application No. 60/666,593 filed on Mar. 31, 2005 in the United States Patent and Trademark Office, the disclosures of which are incorporated herein in their entirety by reference.

TECHNICAL FIELD

The present invention relates to a method and composition for the long-term treatment of gastrointestinal disorders in a human subject.

The present invention also relates to a method and composition for the treatment of gastrointestinal disorders in both male and female human subject.

The present invention further relates to a method and composition for the treatment of gastrointestinal disorders in a human subject aged 65 years and older.

Furthermore, the present invention relates to a method and composition for the improvement of quality of life in a human subject with gastrointestinal disorders.

BACKGROUND ART

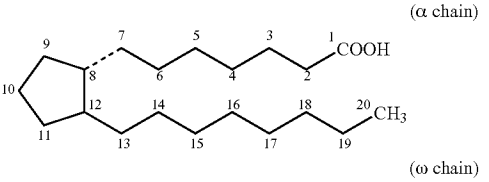
Constipation is generally defined as infrequent and difficult passage of stool. Medical reporting estimates that one of every 50 people in the United States suffers from constipation. That is, one of the most common disorders among Americans. Constipation is more likely to affect females than males and more likely to occur in older adults, showing an exponential increase after the age of 65. The actual occurrence of constipation is likely higher than reported, as many individuals suffer at home without seeking professional care.

Although in some instances constipation may be caused by obstruction, most constipation can be associated with factors such as a diet low in soluble and insoluble fibers, inadequate exercise, medication use (in particular, opiate analgesics, anticholinergic antidepressants, antihistamines, and vinca alkaloids), bowel disorders, neuromuscular disorders, metabolic disorders, poor abdominal pressure or muscular atony.

A precise quantitative definition of constipation has been difficult to establish due to the wide range of perceived "normal" bowel habits, as well as the diverse array of symptoms and signs associated with constipation. The FDA has recognized a need for prescriptive treatment of occasional constipation.

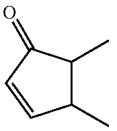
Prostaglandins (hereinafter, referred to as PGs) are members of class of organic carboxylic acids, which are contained in tissues or organs of human or other mammals, and exhibit a wide range of physiological activity. PGs found in nature (primary PGs) generally have a prostanoic acid skeleton as shown in the formula (A):

(A)

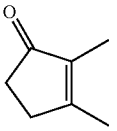


PGs are classified into several types according to the structure and substituents on the five-membered ring, for example,

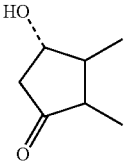
Prostaglandins of the A series (PGAs);



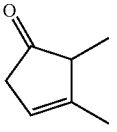
Prostaglandins of the B series (PGBs);



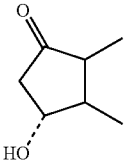
Prostaglandins of the C series (PGCs);



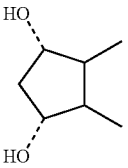
Prostaglandins of the D series (PGDs);



Prostaglandins of the E series (PGEs);



Prostaglandins of the F series (PGFs);



and the like. Further, they are classified into PG_1s containing a 13,14-double bond; PG_2s containing, 5,6- and 13,14-double bonds; and PG_3s containing 5,6-, 13,14- and 17,18-double bonds. PGs are known to have various pharmacological and physiological activities, for example, vasodilatation, inducing of inflammation, platelet aggregation, stimulating uterine muscle, stimulating intestinal muscle, anti-ulcer effect and the like. The major prostaglandins produced in the human gastrointestinal (GI) system are those of the E, I and F series (Sellin, Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management. (WB Saunders Company, 1998); Robert, Physiology of the Gastrointestinal Tract 1407-1434 (Raven, 1981); Rampton, Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids 323-344 (Churchill Livingstone, 1988); Hawkey, et al., *Gastroenterology,* 89: 1162-1188 (1985); Eberhart, et al., Gastroenterology, 109: 285-301 (1995)).

Under normal physiological conditions, endogenously produced prostaglandins play a major role in maintaining GI function, including regulation of intestinal motility and transit, and regulation of fecal consistency. (Sellin, Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management. (WB Saunders Company, 1998); Robert, Physiology of the Gastrointestinal Tract 1407-1434 (Raven, 1981); Rampton, Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids 323-344 (Churchill Livingstone, 1988); Hawkey, et al., *Gastroenterology,* 89: 1162-1188 (1985); Eberhart, et al., *Gastroenterology,* 109: 285-301 (1995); Robert, *Adv Prostaglandin Thromboxane Res,* 2:507-520 (1976); Main, et al., *Postgrad Med J,* 64 Suppl 1: 3-6 (1988); Sanders, *Am J Physiol,* 247: G117 (1984); Pairet, et al., *Am J Physiol.,* 250 (3 pt 1): G302-G308 (1986); Gaginella, Textbook of Secretory Diarrhea 15-30 (Raven Press, 1990)). When administered in pharmacological doses, both PGE_2 and $PGF_{2\alpha}$ have been shown to stimulate intestinal transit and to cause diarrhea (Robert, Physiology of the Gastrointestinal Tract 1407-1434 (Raven, 1981); Rampton, Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids 323-344 (Churchill Livingstone, 1988); Robert, *Adv Prostaglandin Thromboxane Res,* 2:507-520 (1976)). Furthermore, the most commonly reported side effect of misoprostol, a PGE_1 analogue developed for the treatment of peptic ulcer disease, is diarrhea (Monk, et al., Drugs 33 (1): 1-30 (1997))

PGE or PGF can stimulate the intestines and cause intestinal contraction, but the enteropooling effect is poor. Accordingly, it is impossible to use PGEs or PGFs as cathartics because of side effects such as stomachache caused by the intestinal contraction.

Multiple mechanisms, including modifying enteric nerve responses, altering smooth muscle contraction, stimulating mucous secretion, stimulating cellular ionic (in particular electrogenic Cl^- transport) and increasing intestinal fluid volume have been reported to contribute to the GI effects of prostaglandins (Robert, Physiology of the Gastrointestinal Tract 1407-1434 (Raven, 1981); Rampton, Prostaglandins:

Biology and Chemistry of Prostaglandins and Related Eicosanoids 323-344 (Churchill Livingstone, 1988); Hawkey, et al., *Gastroenterology,* 89: 1162-1188 (1985); Eberhart, et al., Gastroenterology, 109: 285-301 (1995); Robert, *Adv Prostaglandin Thromboxane Res,* 2:507-520 (1976); Main, et al., Postgrad Med J, 64 Suppl 1: 3-6 (1988); Sanders, *Am J Physiol,* 247: G117 (1984); Pairet, et al., *Am J Physiol,* 250 (3 pt 1): G302-G308 (1986); Gaginella, Textbook of Secretory Diarrhea 15-30 (Raven Press, 1990); Federal Register Vol. 50, No. 10 (GPO,1985); Pierce, et al., *Gastroenterology* 60 (1): 22-32 (1971); Beubler, et al., *Gastroenterology,* 90: 1972 (1986); Clarke, et al., *Am J Physiol* 259: G62 (1990); Hunt, et al., *J Vet Pharmacol Ther,* 8 (2): 165-173 (1985); Dajani, et al., *Eur J Pharmacol,* 34(1): 105-113 (1975); Sellin, Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management 1451-1471 (WB Saunders Company, 1998)). Prostaglandins have additionally been shown to have cytoprotective effects (Sellin, Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management. (WB Saunders Company, 1998); Robert, *Physiology of the Gastrointestinal Tract* 1407-1434 (Raven, 1981); Robert, *Adv Prostaglandin Thromboxane Res* 2:507-520 (1976); Wallace, et al., Aiiment Pharmacol Ther 9: 227-235 (1995)).

U.S. Pat. No. 5,317,032 to Ueno et al. describes prostaglandin analog cathartics, including the existence of bicyclic tautomers of the same and U.S. Pat. No. 6,414,016 to Ueno describes bicyclic tautomers of a prostaglandin analog as having pronounced activity as anti-constipation agents. The bicyclic tautomers of a prostaglandin analog, which is substituted at the C-16 position by one or more halogen atoms, especially fluorine atoms, can be employed in small doses for relieving constipation.

U.S. Patent publication No. 2003/0130352 to Ueno et al. describes that prostaglandin compound opens and activates chloride channels, especially ClC channels, more especially ClC-2 channel.

U.S. Patent publication No. 2003/0119898 to Ueno et al. describes specific composition of a halogenated prostaglandin analog for the treatment and prevention of constipation.

U.S. Patent publication No. 2004/0138308 to Ueno et al. describes that a chloride channel opener, especially a prostaglandin compound can be used for the treatment of abdominal discomfort, and for the treatment of functional gastrointestinal disorders such as irritable bowel syndrome and functional dyspepsia.

MiraLax™ (polyethylene Glycol 3350, NF Powder for solution) is synthetic polyglycol having an average molecular weight of 3350, and used for the treatment of occasional constipation. This product is basically used for up to two weeks. Prolonged, frequent or excessive use of MiraLax™ may result in electrolyte imbalance and dependence on laxatives (MiraLax™ Package insert). MiraLax™ acts as an osmotic agent, which creates an imbalance in the lumen of the gut and draws fluid osmotically into the lumen. The increased fluid level softens the stool and promotes bowel movements.

Likewise, the aforesaid ClC-2 chloride channel activators are believed to function by stimulating chloride secretion into the lumen of the gut, which draws water through an osmotic mechanism into the lumen that, in turn, promotes bowel movements. Given that a specific prostaglandin compound is an ion channel activator and is believed to work essentially in an osmotic manner, like Miralax™, one would expect that long term use of said prostaglandin compound would also have the disadvantages found in MiraLax™. Therefore, its use would be limited practically to a couple of weeks, just like Miralax™.

Zelnorm® (tegaserod maleate) is indicated for the short-term treatment of women with irritable bowel syndrome (IBS), whose primary bowel symptom is constipation. In two

randomized, placebo-controlled, double-blind studies enrolling 288 males, there were no significant differences between placebo and Zelnorm® response rates. The safety and effectiveness of Zelnorm® in men with IBS with constipation has not been established. In addition, Subgroup analyses of patients aged 65 years and older showed no significant treatment effect for Zelnorm® over placebo. That is, the effectiveness of Zelnorm® in patients aged 65 years and older with chronic idiopathic constipation has not been established. Further, if the patients stop taking Zelnorm®, the symptoms may return within 1 or 2 weeks. (Zelnorm® Package insert)

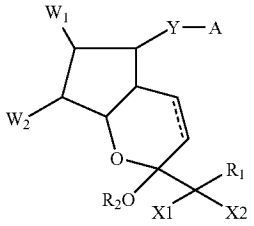
SUMMARY OF THE INVENTION

Despite the essentially osmotic mechanism of action, however, the inventor has found surprisingly that there is no electrolyte shifting on using certain halogenated prostaglandin compounds in human patients during long term use.

The inventor has also found that halogenated prostaglandin compounds are effective in a long-term treatment and that substantially no rebound effect is seen after the discontinuation of even the long-term treatment with said compound.

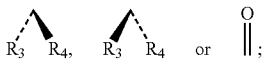
Furthermore, the inventor has found that halogenated prostaglandin compounds improve the quality of life in the patients with gastrointestinal disorders and are similarly effective in treating male and female human patients, and even 65 years and older patients.

Namely, the present invention provides a method for the long term treatment of gastrointestinal disorders in a human subject, which comprises administering an effective amount of a prostaglandin compound represented by Formula (I) and/or its tautomer:



(I)

wherein W_1 and W_2 are



R_3 and R_4 are hydrogen; or one of them is OH and the other is hydrogen;

X_1 and X_2 are hydrogen, lower alkyl or halogen, provided that at least one of them is halogen;

R_2 is hydrogen or alkyl;

Y is a saturated or unsaturated C_{2-10} hydrocarbon chain, which is unsubstituted or substituted by oxo, halogen, alkyl, hydroxy or aryl;

A is —CH_2OH, —$COCH_2OH$, —COOH or its functional derivative;

R_1 is a saturated or unsaturated, straight chain-, branched chain- or ring-forming lower hydrocarbon, which is unsubstituted or substituted by halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, lower cycloalkyl, lower cycloalkyloxy, aryl, or aryloxy; lower cycloalkyl; lower cycloalkyloxy; aryl; or aryloxy;

the bond between C-13 and C-14 positions is double or single bond, and

the steric configuration at C-15 position is R, S or a mixture thereof

to the subject in need thereof.

The present invention also provides a method for the treatment of gastrointestinal disorders in a male human subject, or a human subject aged 65 years and older, which comprises administering an effective amount of a prostaglandin compound represented by Formula (I) and/or its tautomer to the subject in need thereof.

The present invention further provides a method for the improvement of quality of life in a human subject with gastrointestinal disorders, which comprises administering an effective amount of a prostaglandin compound represented by Formula (I) and/or its tautomer to the subject in need thereof.

In each embodiment of the method of the present invention, total daily dose of the PG compound may preferably be 6-96 μg.

The method of the present invention can be carried out by administering a pharmaceutical composition which comprises the above-identified prostaglandin compound and/or its tautomer to the subject to be treated. Accordingly, in another aspect of the present invention, a pharmaceutical composition for the long term treatment of gastrointestinal disorders in a human subject comprising (i) an effective amount of a prostaglandin compound represented by Formula (I) and/or its tautomer and (ii) a pharmaceutically suitable excipient is provided.

The present invention further provides a

Pharmaceutical composition for the treatment of

gastrointestinal disorder in both male and female patients or in a human subject aged 65 years and older, which comprises (i) an effective amount of a prostaglandin compound represented by Formula (I) and/or its tautomer and (ii) a pharmaceutically suitable excipient.

The present invention still further provides a pharmaceutical composition for the improvement of quality of life in a human subject with gastrointestinal disorders, which comprises (i) an effective amount of a prostaglandin compound represented by Formula (I) and/or its tautomer and

(ii) a pharmaceutically suitable excipient.

In another aspect of the present invention, use of a prostaglandin compound represented by Formula (I) and/or its tautomer for the manufacture of a pharmaceutical composition as defined above is provided.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a graph showing severity of constipation during the treatment for 6 months.

FIG. **2** is a graph showing severity of constipation during the treatment for 12 months.

FIG. **3** is a graph showing abdominal bloating during the treatment for 6 months.

FIG. **4** is a graph showing abdominal bloating during the treatment for 12 months.

FIG. **5** is a graph showing abdominal discomfort during the treatment for 6 months.

FIG. **6** is a graph showing abdominal discomfort during the treatment for 12 months.

FIG. **7** is a graph showing effects on bowel movements per week.

FIG. **8** is a graph showing effects on abdominal bloating.

FIG. **9** is a graph showing effects on abdominal discomfort.

FIG. **10** is a graph showing effects on severity of Constipation.

FIG. **11** is a graph showing effects on straining.

FIG. **12** is a graph showing effects on Consistency.

FIG. **13** is a graph showing effects on male vs. female patients in bowel movement.

FIG. **14** is a graph showing effects by age in bowel movement.

DETAILED DESCRIPTION OF THE INVENTION

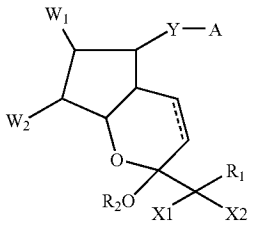
In the present invention, the "effective amount" may be determined based on the age, body weight, conditions of the patient to be treated, desired therapeutic effect, administration route, treatment period and the like. According to the present invention, the amount of the prostaglandin compound to be administered may be 0.001-1000 μg/kg body weight, more preferably, 0.01-100 μg/kg body weight and most preferably, 0.1-10 μg/kg body weight per day. The frequency of administration may be one or more times per day, preferably, two or more times per day. Typical administration amount to a patient is about 6-96 μg per day. According to the specification and claims, the administration amount or dose is determined based on a patient having body weight of approximately 60 kg.

As used herein, the term "about" when used in conjunction with a unit of measure can be defined as +/−30%, preferably +/−20%, and especially +/−10%. For example, the total daily dose of about 6-96 μg preferably means the range of 5.4-105.6 μg. The preferred dose is in the range of about 6-72 μg. In a more preferred embodiment, the dose is in the range of about 6-60 μg. For example, the dose of said halogenated compound can be about 8-48 μg.

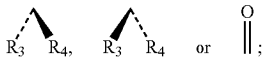
(i) Prostaglandin Compound of Formula (I)

The instant invention utilizes a prostaglandin compound represented by formula (I):

(I)



wherein W_1 and W_2 are



R_3 and R_4 are hydrogen; or one of them is OH and the other is hydrogen;

X_1 and X_2 are hydrogen, lower alkyl or halogen, provided that at least one of them is halogen;

R_2 is hydrogen or alkyl;

Y is a saturated or unsaturated $C_{2\text{-}10}$ hydrocarbon chain, which is unsubstituted or substituted by oxo, halogen, alkyl, hydroxy or aryl;

A is —CH_2OH, —$COCH_2OH$, —COOH or its functional derivative;

R_1 is a saturated or unsaturated, straight chain-, branched chain- or ring-forming lower hydrocarbon, which is unsubstituted or substituted by halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, lower cycloalkyl, lower cycloalkyloxy, aryl, or aryloxy; lower cycloalkyl; lower cycloalkyloxy; aryl; or aryloxy;

the bond between C-13 and C-14 positions is double or single bond, and

the steric configuration at C-15 position is R, S or a mixture thereof.

In the above formula, the term "halogen" is used to include fluorine, chlorine, bromine, and iodine atoms. Particularly preferable halogen atoms for X_1 and X_2 are fluorine atoms.

The term "unsaturated" in the definitions for R_1 and Y is intended to include at least one or more double bonds and/or triple bonds that are isolatedly, separately or serially present between carbon atoms of the main and/or side chains. According to the usual nomenclature, an unsaturated bond between two serial positions is represented by denoting the lower number of the two positions, and an unsaturated bond between two distal positions is represented by denoting both of the positions.

The term "lower" throughout the specification and claims is intended to include a group having 1 to 6 carbon atoms unless otherwise specified.

The term "ring" refers to lower cycloalkyl, lower cycloalkyloxy, aryl or aryloxy.

The term "lower alkyl" refers to a straight or branched chain saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl.

The term "lower alkoxy" refers to a group of lower alkyl-O—, wherein lower alkyl is as defined above.

The term "lower alkanoyloxy" refers to a group represented by the formula RCO—O—, wherein RCO— is an acyl group formed by oxidation of a lower alkyl group as defined above, such as acetyl.

The term "lower cycloalkyl" refers to a cyclic group formed by cyclization of a lower alkyl group as defined above but contains three or more carbon atoms, and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "lower cycloalkyloxy" refers to the group of lower cycloalkyl-O—, wherein lower cycloalkyl is as defined above.

The term "aryl" refers to unsubstituted or substituted aromatic carbocyclic or heterocyclic groups (preferably monocyclic groups), for example, phenyl, naphthyl, tolyl, xylyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, furzanyl, pyranyl, pyridyl, pyridazyl, pyrimidryl, pyrazyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidino, piperazinyl, morpholono, indolyl, benzothienyl, quinolyl, isoquinolyl, puryl, quinazolinyl, carbazolyl, acridinyl, phenathridinyl, benzimidazolyl, benzimidazolonyl, benzothiazolyl and phenothiazinyl. Examples of substituents are halogen atom and halo (lower)alkyl, wherein halogen atom and lower alkyl are as defined above.

The term "aryloxy" refers to a group represented by the formula ArO—, wherein Ar is aryl as defined above.

The term "functional derivative" of A includes salts (preferably pharmaceutically acceptable salts), ethers, esters and amides.

Suitable "pharmaceutically acceptable salts" include conventionally used non-toxic salts, for example a salt with an inorganic base such as an alkali metal salt (such as sodium salt and potassium salt), an alkaline earth metal salt (such as calcium salt and magnesium salt), an ammonium salt; or a salt with an organic base, for example, an amine salt (such as

methylamine salt, dimethylamine salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, tris (hydroxymethylamino)ethane salt, monomethyl-monoethanolamine salt, procaine salt and caffeine salt), a basic amino acid salt (such as arginine salt and lysine salt), tetraalkyl ammonium salt and the like. These salts may be prepared by a conventional process, for example from the corresponding acid and base or by salt interchange.

Examples of the ethers include alkyl ethers, for example, lower alkyl ethers such as methyl ether, ethyl ether, propyl ether, isopropyl ether, butyl ether, isobutyl ether, t-butyl ether, pentyl ether and 1-cyclopropyl ethyl ether; and medium or higher alkyl ethers such as octyl ether, diethylhexyl ether, lauryl ether and cetyl ether; unsaturated ethers such as oleyl ether and linolenyl ether; lower alkenyl ethers such as vinyl ether, allyl ether; lower alkynyl ethers such as ethynyl ether and propynyl ether; hydroxy(lower)alkyl ethers such as hydroxyethyl ether and hydroxyisopropyl ether; lower alkoxy (lower)alkyl ethers such as methoxymethyl ether and 1-methoxyethyl ether; optionally substituted aryl ethers such as phenyl ether, tosyl ether, t-butylphenyl ether, salicyl ether, 3,4-di-methoxyphenyl ether and benzamidophenyl ether; and aryl(lower)alkyl ethers such as benzyl ether, trityl ether and benzhydryl ether.

Examples of the esters include aliphatic esters, for example, lower alkyl esters such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester and 1-cyclopropylethyl ester; lower alkenyl esters such as vinyl ester and allyl ester; lower alkynyl esters such as ethynyl ester and propynyl ester; hydroxy(lower) alkyl ester such as hydroxyethyl ester; lower alkoxy (lower) alkyl esters such as methoxymethyl ester and 1-methoxyethyl ester; and optionally substituted aryl esters such as, for example, phenyl ester, tolyl ester, t-butylphenyl ester, salicyl ester, 3,4-di-methoxyphenyl ester and benzamidophenyl ester; and aryl(lower)alkyl ester such as benzyl ester, trityl ester and benzhydryl ester.

The amide of A means a group represented by the formula —CONR'R", wherein each of R' and R" is hydrogen, lower alkyl, aryl, alkyl- or aryl-sulfonyl, lower alkenyl and lower alkynyl, and includes for example, lower alkyl amides such as methylamide, ethylamide, dimethylamide and diethylamide; arylamides such as anilide and toluidide; and alkyl- or aryl-sulfonylamides such as methylsulfonylamide, ethylsulfonylamide and tolylsulfonylamide.

Examples of Y include, for example, the following groups:

—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH=CH—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH=CH—,
—CH_2—C≡C—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—O—CH_2—,
—CH_2—CH=CH—CH_2—O—CH_2—,
—CH_2—C≡C—CH_2—O—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH=CH—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—CH=CH—,
—CH_2—C≡C—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—CH (CH_3)—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH (CH_3)—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH=CH—CH_2—CH_2—CH_2—CH_2—CH_2—,
—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH=CH—,
—CH_2—C≡C—CH_2—CH_2—CH_2—CH_2—CH_2—, and
—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH (CH_3)—CH_2—.

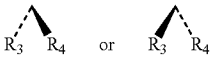
Further, at least one carbon atom in the aliphatic hydrocarbon of Y is optionally substituted by oxygen, nitrogen or sulfur.

Preferred A is —COOH or its pharmaceutically acceptable salt or ester.

Preferred X_1 and X_2 are both being halogen atoms, and more preferably, fluorine atoms.

Preferred W_1 is =O.

Preferred W_2 is



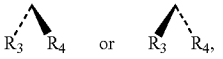
where R_3 and R_4 are both hydrogen atoms.

Preferred Y is an unsubstituted, saturated or unsaturated hydrocarbon chain having 6-8 carbon atoms.

Preferred R_1 is a hydrocarbon containing 1-6 carbon atoms, more preferably, 1-4 carbon atoms. R_1 may have one or two side chains having one carbon atom.

R_2 is preferably hydrogen.

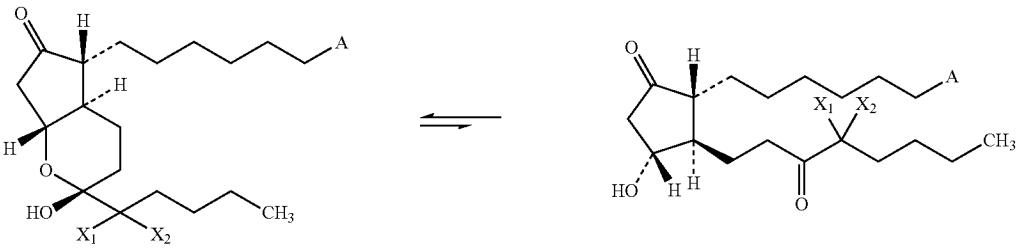
Most preferred embodiment is a prostaglandin compound of formula (I) in which A is —COOH; Y is $(CH_2)_6$; W_1 is =O; W_2 is



wherein R_3 and R_4 are both hydrogen; R_2 is hydrogen; X_1 and X_2 are fluorine; and R_1 is $(CH_2)_3CH_3$ or $CH_2CH(CH_3)CH_2CH_3$.

The active agent of this invention or the PG compound of formula (I) exists as a bicyclic compound in a solid state, but when dissolved in a solvent, a part of the compound forms a tautomer. In the absence of water, compound represented by formula (I) exists predominantly in the form of the bicyclic structure. In aqueous media, it is believed that hydrogen bonding occurs between the water molecule and, for example, the keto moiety at the C-15 position, thereby hindering bicyclic ring formation. In addition, it is believed that the halogen atoms at the C-16 position promote bicyclic ring formation. The tautomerism between the hydroxy at the C-11 position and the keto moiety at the C-15 position, shown below, is especially significant in the case of compounds having a 13,14 single bond and two fluorine atoms at the C-16 position.

Accordingly, the present invention may comprise isomers of the halogenated prostaglandin compounds. For example, mono-cyclic tautomers having a keto group at the C-15 position and halogen atoms at the C-16 position is shown as follows.



bicyclic form

monocyclic form

A preferred compound according to the invention in its monocyclic form can be named as 13,14-dihydro-15-keto-16, 16-difluoro-PGE_1, according to conventional prostaglandin nomenclature.

(ii) The Pharmaceutically Suitable Excipient

According to the invention, the pharmaceutical composition may be formulated in any form. The pharmaceutically suitable excipient may be, therefore, selected depending on the desired form of the composition. According to the invention, "pharmaceutically suitable excipient" means an inert substance, which is combined with the active ingredient of the invention and suitable for preparing the desired form.

For example, a solid composition for oral administration of the present invention may include tablets, preparations, granules and the like. In such a solid composition, one or more active ingredients may be mixed with at least one inactive diluent, for example, lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinyl pyrrolidone, magnesium aluminate metasilicate and the like. According to the usual work-up, the composition may contain additives other than inactive diluent, for example, lubricant such as magnesium stearate; disintegrant such as fibrous calcium gluconate; stabilizer such as cyclodextrin, for example, α,β- or γ-cyclodextrin; etherified cyclodextrin such as dimethyl-α-, dimethyl-β-, trimethyl-β-, or hydroxypropyl-β-cyclodextrin; branched cyclodextrin such as glucosyl-, maltosyl-cyclodextrin; formylated cyclodextrin, cyclodextrin containing sulfur; phospholipid and the like. When the above cyclodextrins are used, inclusion compound with cyclodextrins may be sometimes formed to enhance stability. Alternatively, phospholipid may be sometimes used to form liposome, resulting in enhanced stability.

Tablets or pills may be coated with film soluble in the stomach or intestine such as sugar, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose phthalate as needed. Further, they may be formed as capsules with absorbable substances such as gelatins. Preferably, the composition is formulated in a soft gelatin capsule with liquid contents of the halogenated prostaglandin compound and a medium chain fatty acid triglyceride. Examples of the medium chain fatty acid triglyceride used in the present invention include a triglyceride of a saturated or unsaturated fatty acid having 6-14 carbon atoms which may have a branched chain. A preferred fatty acid is a straight chain saturated fatty acid, for example caproic acid (C6), caprylic acid (C8), capric acid (C10), lauric acid (C12) and myristic acid (C14). In addition, two or more medium chain fatty acid triglycerides may be used in combination. Further suitable excipients are disclosed in the published PCT application WO 01/27099.

A liquid composition for oral administration may be in the form of emulsion, solution, suspension, syrup or elixir comprising a generally used inactive diluent. Such composition may contain, in addition to the inactive diluent, additives such as lubricants, sweetening agents, flavoring agents, preservatives, solubilizers, anti-oxidants and the like. The additives may be selected from those described in any general textbooks in the pharmaceutical field. Such liquid compositions may be directly enclosed in soft capsules. The composition of the present invention may be suppository, enema or the like. They may be in the form of, for example, sterile aqueous or non-aqueous solution, suspension, emulsion, and the like. Examples of the excipients for the aqueous solution, suspension or emulsion may include, for example, distilled water, physiological saline and Ringer's solution.

Examples of excipients for non-aqueous solution, suspension or emulsion may include, for example, propylene glycol, polyethylene glycol, fatty acid triglyceride, vegetable oil such as olive oil, alcohols such as ethanol, polysorbate and the like. Such composition may contain additives such as preservatives, wetting agent, emulsifier, dispersant, anti-oxidants and the like.

According to the present invention, the pharmaceutical composition may be either for parenteral or oral administration and an orally applicable composition is preferred. In an example, the active ingredient is preferably dissolved medium chain fatty acid triglyceride and filled in a capsule.

According to the method of the invention, the composition of the present invention can be administered systemically or locally by means of oral or parenteral administration, including parenteral administration using suppository, enema and the like. The composition of the present invention may be administered once to several times per day.

Preferably, the total daily dose of the prostaglandin compound of the present invention is in the range of about 6-96 μg, more preferably about 6-72 μg, still more preferably about 6-60 μg and especially, 8-48 μg. The dose may vary somewhat, at the discretion of the physician, depending the age and body weight of the patient, conditions, therapeutic effect, administration route, treatment period and the like.

The term "substantially no electrolyte shifting" used herein means that electrolyte imbalance during the term of the treatment is far less than that induced by a known electrolyte imbalance inducing agent. Moreover, the term "substantially no electrolyte shifting" refers to serum electrolyte levels in a treated patient that are within clinically normal ranges as they would be understood by the clinician. As described above, MiraLax™, that is used for the treatment of constipation may induce electrolyte imbalance, which can result in, among other things, dangerous cardiac problems. On the other hand, as shown in the following example, the prostaglandin compound used in the instant invention induces substantially no electrolyte shifting even if it is administered for long term.

The following examples also show that the pharmaceutical composition of the present invention induces substantially no rebound constipation or the other disadvantage after stopping the prolonged treatment with the composition. Accordingly, it

can be resulted in that the composition of the present invention is useful for long term treatment.

Furthermore, the assessment of quality of life in both constipation and IBS patients observed that the present compounds improved the quality of life in the patients.

According to the present invention, the present compounds are useful for the long-term treatment of gastrointestinal disorders. It is similarly effective in treating male and female patients. In addition it is useful in treating a patient aged 65 years and older.

The "gastrointestinal disorders" used herein include for example, but not limited to, acute or chronic constipation, functional gastrointestinal disorders such as irritable bowel syndrome and functional dyspepsia, gastric ulcer, large or small intestinal ulcer and abdominal discomfort.

Included in the types of constipation to be treated, although not particularly limited, are functional constipation such as relaxing constipation, spastic constipation, rectal constipation and post operative ileus; organic constipation caused by intestinal diseases and stenosis due to postoperative adhesion; and constipation induced by a drug such as opioid.

In addition to relieving or preventing constipation, the present composition may be used for preventing a patient with hernia or cardiovascular diseases from straining at stool, or for softening feces of a patient with anorectal diseases. Moreover, the present composition may be used for cleansing the gastrointestinal tract in preparation for endoscopic examination or for diagnostic or surgical procedures such as colonoscopy, barium enema X-rays and intravenous pyelography, and emergency procedures such as emergency gastrointestinal flush for poison removal and the like. Accordingly the invention covers embodiments wherein the composition of the present invention is used for cleansing the gastrointestinal tract in a human male subject or a human subject aged 65 years and older in need thereof.

The term "treatment" used herein includes any means of control such as prevention, care, relief of symptoms, attenuation of symptoms and arrest of progression. The term "long term treatment" used herein means administering the compound for at least two weeks. The compound may be administered everyday for the whole term of the treatment or with an interval of one to several days. In a particular embodiment of the present invention, the prostaglandin compound is administered for at least three weeks. In another particular embodiment, the prostaglandin compound is administered for at least four weeks. In another particular embodiment, the prostaglandin compound is administered for at least 2 months. In another particular embodiment, the prostaglandin compound is administered for at least 6 months.

The further details of the present invention will follow with reference to test examples, which, however, are not intended to limit the present invention.

Example 1

(Method)

Multi-center, open-label study was performed to evaluate the safety of 48 μg of Compound A (13,14-dihydro-15-keto-16,16-difluoro-PGE_1) (24 μg of Compound A b.i.d) when administered daily for 24 weeks (6 months) or 48 weeks (12 months) to subjects with occasional constipation. Patients who demonstrated history of chronic constipation for at least 3 months (having less then three SBMs per week) and at least one associated symptom such as hard stools, incomplete evacuation, straining were enrolled. After 14-day drug-free washout period, they received 48 μg of Compound A (24 μg of Compound A b.i.d) orally for 48 weeks.

In this study, the following parameters were evaluated.

1) Electrolyte Balance

Sodium, potassium, chloride, calcium, magnesium and phosphorus ion concentrations in serum of patients (n=299) were measured before, and at 6, 12, 18, 24, 30, 36, 48 and 50 weeks after the start of the Compound A treatment.

The laboratory standard values for the panel of electrolytes were taken from the normal reference ranges for the central laboratory.

2) Severity of Constipation, 3) Abdominal Bloating and 4) Abdominal Discomfort

Each parameter (Severity of Constipation, Abdominal bloating or Abdominal discomfort) was evaluated on the scale of: 0 (absent), 1 (mild), 2 (moderate), 3 (severe) and 4 (very severe) in the patients during 6 months (n=246) or 12 months (n=304) treatments.

(Results)

1) Electrolyte Balance

As shown in Table 1, treatment with compound A had no effect on sodium, potassium, chloride, calcium, magnesium and phosphorus ion concentration in serum of the patients. The results demonstrate that Compound A does not induce substantial shift of electrolyte over long-term administration.

TABLE 1

Mean Serum Chemistry Results						
Week	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Calcium (mg/dL)	Magnesium (mg/dL)	Phosphorus (mg/dL)
0	141.00	4.28	103.08	9.61	2.18	3.65
6	142.25	4.28	103.00	9.90	2.23	3.20
12	139.78	4.20	103.08	9.71	2.24	3.57
18	141.50	4.40	105.50	9.30	2.35	3.55
24	139.21	4.19	102.56	9.77	2.21	3.61
30	136.00	4.30	100.00	9.10	2.30	2.50
36	138.94	4.18	102.51	9.67	2.19	3.58
48	139.59	4.20	102.88	9.66	2.14	3.50
50	139.11	4.49	102.67	9.47	2.31	3.54
Laboratory Standard	135-148	3.5-5.5	96-109	8.5-10.6	1.6-2.6	*

*Female: 15-19 year 2.5-5.3 mg/dL, ≥20 year 2.5-4.5 mg/dL
Male: 15-19 year 2.5-5.6 mg/dL, ≥20 year 2.5-4.5 mg/dL

2) Severity of Constipation (6 and 12 months), 3) Abdominal bloating (6 and 12 months) and 4) Abdominal discomfort (6 and 12 months) were shown in FIG. **1** to FIG. **6** respectively.

As shown in FIGS. **1** to **6**, Compound A is effective during the 6 months and 12 months treatment.

Example 2

(Method)

Multi-center, double-blind, randomized, placebo-controlled study was performed to assess post-treatment response, in a portion of the total population, after four (4) weeks of active treatment (48 μg Compound A total daily dose) and three (3) weeks randomized withdrawal period. Patients who demonstrated history of chronic constipation for at least 6 months (having less then three SBMs per week) and at least one associated symptom such as hard stools, incomplete evacuation, straining were enrolled. After 14-day drug-free washout period, they received orally 48 μg (total daily dose) of Compound A for 28 days followed by either 0 or 48 μg (total daily dose) of Compound A for 21 days.

In this study, the following parameters were evaluated.

1) Bowel movements per week

2) Abdominal bloating

3) Abdominal discomfort

4) Severity of Constipation

5) Straining

6) Consistency

Each parameter (Abdominal bloating, Abdominal discomfort, Severity of Constipation or Straining) was evaluated on the scale of: 0 (absent), 1 (mild), 2 (moderate), 3 (severe) and 4 (very severe) in the patients. Consistency was evaluated on a scale of: 0 (very loose), 1 (loose), 2 (normal), 3 (hard) and 4 (very hard, little balls)

(Results)

1) Bowel movements per week, 2) Abdominal bloating, 3) Abdominal discomfort, 4) Severity of Constipation, 5) Straining and 6) Consistency were shown in FIG. **7** to FIG. **12** respectively.

As shown in FIGS. **7** to **12**, substantially no rebound effect after the discontinuation of the treatment with Compound A was observed, and the efficacy of the compound A was sustained even after stopping the treatment.

This result indicates that the quality of life of the patients is improved by the administration of compound A.

Example 3

(Method)

Patients with irritable bowel syndrome (IBS) were treated with 48 μg of Compound A (24 μg of Compound A b.i.d) for 48 weeks.

In this study, we evaluated the following parameters.

1) Abdominal discomfort

2) Abdominal bloating

3) Severity of Constipation

Each of Abdominal discomfort and Abdominal bloating was evaluated on a scale of: 0 (absent), 1 (mild), 2 (moderate), 3 (severe) and 4 (very severe) in the patients. Severity of Constipation was evaluated on a scale of: 0 (very loose), 1: (loose), 2: (normal), 3 (hard), 4 (very hard) in the patients.

(Results)

1) Abdominal discomfort, 2) Abdominal bloating and 3) Severity of Constipation were shown in Table 2 to Table 4 respectively.

As shown in Tables 2 to 4, Compound A is effective during the 12 months treatment in IBS patients.

TABLE 2

Analysis of Abdominal discomfort

Week	Compound A Mean ± SD (N) Median Range	Compound A Mean ± SD (N) Median Range p-Value*
Baseline	1.95 ± 0.850 (183) 2.00 0.00-4.00	Change from Baseline
Week 12	1.16 ± 0.836 (135) 1.00 0.00-4.00	−0.79 ± 0.993 (135) −1.00 −3.00-2.00 <0.001#
Week 18	0.98 ± 0.874 (111) 1.00 0.00-3.00	−0.97 ± 1.031 (111) −1.00 −4.00-3.00 <0.001#
Week 24	1.09 ± 0.917 (107) 1.00 0.00-4.00	−0.82 ± 1.035 (107) −1.00 −4.00-3.00 <0.001#
Week 36	0.93 ± 0.799 (57) 1.00 0.00-3.00	−0.77 ± 0.926 (57) −1.00 −4.00-2.00 <0.001#
Week 48	0.87 ± 0.929 (52) 1.00 0.00-4.00	−0.81 ± 0.908 (52) −1.00 −2.00-2.00 <0.001#
End of Treatment	1.28 ± 1.020 (183) 1.00 0.00-4.00	−0.66 ± 1.112 (183) −1.00 −4.00-2.00 <0.001#
Follow-Up	1.40 ± 0.996 (121) 1.00 0.00-4.00	−0.55 ± 1.080 (121) −1.00 −4.00-2.00 <0.001#

*P-value is from a Wilcoxon signed-rank test.

TABLE 3

Analysis of Abdominal bloating

Week	Compound A Mean ± SD (N) Median Range	Compound A Mean ± SD (N) Median Range p-Value*
Baseline	2.23 ± 0.927 (183) 2.00 0.00-4.00	Change from Baseline
Week 12	1.43 ± 0.919 (135) 1.00 0.00-4.00	−0.84 ± 1.045 (135) −1.00 −3.00-3.00 <0.001#
Week 18	1.19 ± 0.837 (111) 1.00 0.00-3.00	−1.07 ± 1.068 (111) −1.00 −3.00-3.00 <0.001#
Week 24	1.26 ± 0.915 (107) 1.00 0.00-4.00	−0.95 ± 1.102 (107) −1.00 −4.00-3.00 <0.001#
Week 36	1.05 ± 0.854 (57) 1.00 0.00-3.00	−1.00 ± 1.134 (57) −1.00 −4.00-2.00 <0.001#
Week 48	1.12 ± 0.832 (52) 1.00 0.00-4.00	−0.94 ± 0.802 (52) −1.00 −3.00-1.00 <0.001#
End of Treatment	1.50 ± 1.005 (183) 1.00 0.00-4.00	−0.73 ± 1.075 (183) −1.00 −4.00-2.00 <0.001#

TABLE 3-continued

Analysis of Abdominal bloating

Week	Compound A Mean ± SD (N) Median Range	Compound A Mean ± SD (N) Median Range p-Value*
Follow-Up	1.55 ± 0.957 (121) 2.00 0.00-4.00	−0.69 ± 1.109 (121) −1.00 −3.00-3.00 <0.001#

*P-value is from a Wilcoxon signed-rank test.

TABLE 4

Analysis of Severity of Constipation

Week	Compound A Mean ± SD (N) Median Range	Compound A Mean ± SD (N) Median Range p-Value*
Baseline	2.95 ± 0.751 (183) 3.00 1.00-4.00	Change from Baseline
Week 12	1.76 ± 1.003 (135) 2.00 0.00-4.00	−1.16 ± 1.099 (135) −1.00 −4.00-2.00 <0.001#
Week 18	1.33 ± 0.985 (111) 1.00 0.00-4.00	−1.59 ± 1.148 (111) −2.00 −4.00-3.00 <0.001#
Week 24	1.50 ± 0.965 (107) 1.00 0.00-4.00	−1.40 ± 1.036 (107) −1.00 −3.00-2.00 <0.001#
Week 36	1.39 ± 0.921 (57) 1.00 0.00-4.00	−1.33 ± 1.123 (57) −1.00 −4.00-2.00 <0.001#
Week 48	1.37 ± 0.894 (51) 1.00 0.00-3.00	−1.37 ± 1.095 (51) −1.00 −3.00-1.00 <0.001#
End of Treatment	1.84 ± 1.120 (183) 2.00 0.00-4.00	−1.11 ± 1.148 (183) −1.00 −4.00-2.00 <0.001#
Follow-Up	2.07 ± 0.946 (121) 2.00 0.00-4.00	−0.88 ± 1.122 (121) −1.00 −4.00-2.00 <0.001#

*P-value is from a Wilcoxon signed-rank test.

Example 4

(Method)

Multi-center, parallel-group, double-blind, placebo-controlled study was performed to compare the effect of Compound A on the weekly number of spontaneous bowel movements in male and female patients. Male and female patients with occasional constipation were received 48 μg (total daily dose) of Compound A (24 μg of Compound A b.i.d) for 4 weeks. The bowel movements in the patient were recorded during the treatment.

(Results)

The effect of 48 μg of Compound A on the weekly number of spontaneous bowel movements in male vs. female patients is shown in FIG. **13**.

As shown in FIG. **13**, Compound A was significantly effective for both male and female patients. There was no significant difference between the effects in male and female patients.

Example 5

(Method)

Multi-center, parallel-group, double-blind, placebo-controlled study was performed to compare the effect of Compound A on improving weekly number of spontaneous bowel movements among different aged patients with occasional constipation. The patients were received 48 μg (total daily dose) of Compound A (24 μg of Compound A b.i.d) for 4 weeks. The bowel movements in the patient were recorded during the treatment.

(Results)

The result is shown in FIG. **14**. As shown in FIG. **14**, Compound A was significantly effective in all aged groups, and even 65 years and older patients.

Example 6

(Method)

A 48-week multi-center study was performed to assess the safety and efficacy of 48 μg (total daily dose) of Compound A to subjects with occasional constipation. Patients who demonstrated history of constipation for at least 3 months (having less then three SBMs per week) and at least one associated symptom such as hard stools, incomplete evacuation, straining were enrolled. After 14-day drug-free washout period, they received orally 48 μg of Compound A (24 μg of Compound 1, b.i.d) daily for 48 weeks.

The subjects completed the Medical Outcomes Study (MOS) 36-item short form (SF-36), i.e., a conventionally used QOL assessment form, at enrollment (baseline) and end of treatment (Week 48). Components of the MOS SF-36 (Med Care 30(6),473-483, 1992) are outlined below:

Physical component: Physical Function; Role-Physical, Bodily Pain and General Health

Mental component: Vitality, Social Function, Role-Emotional and Mental Health

Each of the 8 components was scored within the guidelines of the publisher, including the publisher's guidelines for imputing missing variables. The change from baseline in each of the 8 component scores at the end of treatment (Week 48) were recorded and evaluated with paired t-tests.

(Results)

As shown in Table 5, for each of the 8 component scores, the mean baseline score was between 47 and 52, indicating that the subject population was generally healthy. The mean change from baseline for each component score at Week 48 represented a small increase, which is indicative of an improvement in the respective categories. Improvements that were significantly different from zero were observed at Week 48 for the components of Physical Function, Role-Physical, Bodily Pain, General Health, Vitality, Social Function and Mental Health. The results indicate that Compound A improves the QOL of the patients.

TABLE 5

Summary of SF36 results

	Component/Scale Score							
	Physical Function	Role-Physical	Bodily Pain	General Health	Vitality	Social Function	Role-Emotional	Mental Health
Baseline								
N	320	320	319	319	319	320	319	319
Mean	49.04	49.75	47.53	51.52	50.61	50.12	49.52	50.60
(Std)	9.817	9.457	9.765	9.069	9.940	9.778	9.973	9.829
Week 48[a)]								
N	153	153	151	151	151	152	151	151
Mean [b)]	2.48**	1.95**	3.38**	1.47*	2.89**	2.22**	1.22	1.97**
(Std)	8.431	7.403	9.883	7.827	9.163	8.973	9.560	9.201

[a)]Values represented at Week 48 are for the changes from baseline.
[b)] *p < 0.05, **P < 0.01 (paired T-tests.)

Example 7

(Method)

A 12-week, double-blind, randomized study was performed to assess the safety and efficacy of oral 16 μg, 32 μg and 48 μg (total daily dose) of compound A to subjects with irritable bowel syndrome (IBS).

The patients answered the IBS QOL questionnaire at baseline, at week 4, Week 12 and at the end of study, and Questionnaire results were scored according to the IBS QOL User's Manual (A Quality of Life Measure for Persons with Irritable Bowel Syndrome (IBS-QOL): User's Manual and Scoring Diskette for United States Version. Seattle, Wash.: University of Washington; 1997). Scaled scores were used for all analyses, and scores were calculated according to the User's Manual as follows:

Scaled Score=([Sum of IBS-QOL items−lowest possible score]/Possible raw score range))×100

Changes from baseline at week 4, week 12 and at the End of Study were assessed for the mean overall score and for the mean domain scores (dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual, and relationship).

(Results)

A summary of mean change from baseline in IBS-QOL scores analyzed without LOCF (Last observation carried forward) is shown in Table 6 to Table 8.

These data indicated that the change from baseline was significantly different from Zero in all groups. In general, the 16 μg of compound A group showed the greatest improvement from baseline of all the groups in every specific area and for QOL overall.

TABLE 6

Summary of change from Baseline in IBS QOL (16 μg)

	Component/Scaled Score								
	QOL Overall	Dysphoria	Interference with Activity	Body Image	Health Worry	Food Avoidance	Social Reaction	Sexual	Relationship
Baseline									
N	51	51	51	51	51	51	51	51	51
Mean	55.66	53.19	65.82	41.42	37.74	46.08	63.97	64.95	67.81
(Std)	21.165	27.333	22.544	22.877	23.113	30.016	24.546	33.913	25.387
Week 4									
N	45	45	45	45	45	45	45	45	45
Mean	14.7**	17.85**	10.87**	16.39**	22.41**	13.89**	11.94**	13.33**	10.74**
(Std)	14.842	18.483	14.899	19.867	20.241	22.332	19.439	25.057	17.463
Week 12									
N	42	42	42	42	42	42	42	42	42
Mean	18.54**	23.51**	13.95**	22.32**	23.81**	15.28**	14.58**	16.67**	15.47**
(Std)	17.698	20.949	18.392	21.701	22.129	26.792	21.548	29.82	21.897
End of Study									
N	49	49	49	49	49	49	49	49	49
Mean	16.82**	21.62**	11.95**	20.41**	21.94**	13.95**	13.78**	14.03**	14.28**
(Std)	17.145	20.451	18.348	21.491	21.562	25.762	20.57	28.485	20.692

TABLE 7

Summary of change from Baseline in IBS QOL (32 μg)

	Component/Scale Score								
	QOL Overall	Dysphoria	Interference with Activity	Body Image	Health Worry	Food Avoidance	Social Reaction	Sexual	Relationship
Baseline									
N	49	49	49	49	49	49	49	49	49
Mean	60.14	59.69	69.82	43.37	44.38	52.21	66.84	68.62	70.23
(Std)	22.05	24.79	23.385	24.387	24.672	32.175	28.562	31.367	23.385
Week 4									
N	36	36	36	36	36	36	36	36	36
Mean	11.25**	14.58**	7.04*	15.28**	16.9**	8.33*	9.9**	8.68**	7.64*
(Std)	16.277	20.39	17.753	18.264	17.534	23.988	16.46	18.131	18.831
Week 12									
N	33	33	33	33	33	33	33	33	33
Mean	13.08**	15.25**	9.42**	17.99**	19.44**	11.36**	10.8**	10.98**	9.09*
(Std)	13.527	15.285	18.052	15.21	21.616	23.46	14.173	18.424	20.87
End of Study									
N	44	44	44	44	44	44	44	44	44
Mean	12.58**	14.77**	8.2**	17.47**	17.61**	10.79**	11.08**	10.23**	10.79**
(Std)	12.621	14.429	16.726	15.344	22.317	21.906	14.32	16.894	20.139

TABLE 8

Summary of change from Baseline in IBS QOL (48 μg)

	Component/Scaled Score								
	QOL Overall	Dysphoria	Interference with Activity	Body Image	Health Worry	Food Avoidance	Social Reaction	Sexual	Relationship
Baseline									
N	45	45	45	45	45	45	45	45	45
Mean	59.85	56.81	68.25	45.69	44.07	50.37	66.81	71.94	75.18
(Std)	21.664	26.802	23.396	21.396	23.274	31.927	27.074	30.404	22.365
Week 4									
N	34	34	34	34	34	34	34	34	34
Mean	12.43**	17.28**	9.14**	13.24**	19.61**	12.01**	8.82**	8.46**	6.87**
(Std)	11.619	16.842	14.477	13.568	18.562	19.59	14.028	15.607	12.558
Week 12									
N	30	30	30	30	30	30	30	30	30
Mean	14.8**	20.83**	10.95**	17.08**	23.33**	11.3**9	14.17**	5	6.95**
(Std)	13.65	18.863	15.091	18.419	18.098	22.153	21.143	18.159	12.202
End of Study									
N	43	43	43	43	43	43	43	43	43
Mean	11.54**	16.28**	7.97**	14.24**	17.05**	8.33**	12.06**	3.49	6.01**
(Std)	13.002	18.62	14.387	17.43	19.067	20.002	18.72	17.535	12.244

*P < 0.05,
**P < 0.01 (paired T-Tests)

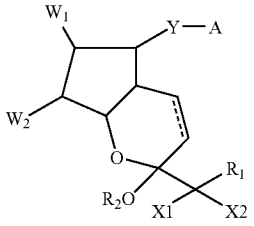
The description of the invention is merely exemplary in nature and, thus, variations that do not depart from the gist of the invention are intended to be within the scope of the invention. Such variations are not to be regarded as a departure from the spirit and scope of the invention.

All patents and publications cited in this specification are herein incorporated by reference

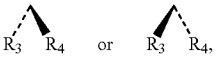
What is claimed is:

1. A method for the long term treatment of chronic constipation in a human subject, wherein the treatment comprises administering to the subject in need thereof an effective amount of a prostaglandin compound represented by Formula (I) and/or its tautomer:

(I)



wherein W_1 is =O; and W_2 is



wherein R_3 and R_4 are hydrogen;

X_1 and X_2 are halogen;

R_2 is hydrogen or alkyl;

Y is a saturated or unsaturated $C_{2\text{-}10}$ hydrocarbon chain;

A is —COOH or its salt, ester or amide;

R1 is a saturated or unsaturated, straight chain or branched chain lower hydrocarbon;

the bond between C-13 and C-14 positions is double or single bond, and

the steric configuration at C-15 position is R, S or a mixture thereof,

wherein said prostaglandin compound is administered for over 4 weeks,

wherein the treatment induces substantially no serum electrolyte shifting during the term of treatment,

wherein the amount of said prostaglandin compound to be administered is in the range of about 6-48 μg per day, and

wherein the treatment improves quality of life of the subject.

2. The method of claim **1**, wherein said prostaglandin compound is a monocyclic tautomer of formula (I).

3. The method of claim **1**, wherein the amount of said prostaglandin compound to be administered is in the range of about 6-32 μg per day.

4. The method of claim **1**, wherein the amount of said prostaglandin compound to be administered is in the range of about 6-16 μg per day.

5. The method of claim **1**, wherein the amount of said prostaglandin compound to be administered is in the range of about 8-48 μg per day.

6. The method of claim **1**, wherein the prostaglandin compound is administered orally.

7. The method of claim **6**, wherein said prostaglandin compound is administered with an oil solvent as an excipient.

8. The method of claim **7**, wherein said oil solvent is a medium chain fatty acid triglyceride.

9. The method of claim **1**, wherein A is —COOH; Y is $(CH_2)_6$; atoms; R_2 is hydrogen atom; X_1 and X_2 are fluorine atoms; and R_1 is $(CH_2)_3CH_3$.

10. The method of claim **1**, wherein said prostaglandin compound is administered for at least 6 months.

11. The method of claim **1**, wherein said prostaglandin compound is administered for at least 1 year.

12. The method of claim **1**, wherein said human subject is a male human subject.

13. The method of claim **1**, wherein said human subject is a human subject aged 65 years and older.

14. The method of claim **1**, wherein A is —COOH; Y is $(CH_2)_6$; atoms; R_2 is hydrogen atom; X_1 and X_2 are fluorine atoms; and R_1 is $CH_2CH(CH_3)CH_2CH_3$.

15. The method of claim **1**, wherein said human subject is aged 18 years or older.

16. The method of claim **1**, wherein said prostaglandin compound is administered for at least 2 months.

17. The method of claim **1**, wherein the treatment improves quality of life of the subject that is confirmed by SF-36.

* * * * *